



US009140692B1

(12) **United States Patent**  
**Nudelman**

(10) **Patent No.:** **US 9,140,692 B1**  
(45) **Date of Patent:** **Sep. 22, 2015**

(54) **METHODS OF IDENTIFYING  
GLYCOPEPTIDES RECOGNIZED BY  
DISEASE-ASSOCIATED AUTO-ANTIBODIES**

(75) Inventor: **Edward Nudelman**, Beverly, MA (US)

(73) Assignee: **Glycozym, Inc.**, Beverly, MA (US)

(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 271 days.

(21) Appl. No.: **12/987,034**

(22) Filed: **Jan. 7, 2011**

**Related U.S. Application Data**

(60) Provisional application No. 61/293,583, filed on Jan. 8, 2010, provisional application No. 61/294,477, filed on Jan. 12, 2010.

(51) **Int. Cl.**  
**G01N 33/53** (2006.01)

(52) **U.S. Cl.**  
CPC ..... **G01N 33/53** (2013.01)

(58) **Field of Classification Search**  
None  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,946,778	A	8/1990	Ladner et al.	
5,132,405	A	7/1992	Huston et al.	
5,476,786	A	12/1995	Huston	
5,876,716	A	3/1999	Hansen et al.	
6,465,220	B1	10/2002	Hassan et al.	
7,332,279	B2	2/2008	Clausen et al.	
2013/0059744	A1*	3/2013	Wandall et al.	506/9

**FOREIGN PATENT DOCUMENTS**

WO	89/12690	A1	12/1989
WO	WO0190197	*	11/2001
WO	WO03099193	*	12/2003
WO	WO2005015206	*	2/2005

**OTHER PUBLICATIONS**

Backlund et al., "Glycosylation of type II collagen is of major importance for T cell tolerance and pathology in collagen-induced arthritis", *Eur J Immunol*, 32:3776-3784 (2002).

Bennett et al., "cDNA cloning and expression of a novel human UDP-N-acetyl-alpha-D-galactosamine—Polypeptide N-acetylgalactosaminyltransferase, GalNAc-T3", *Journal of Biological Chemistry*, 271:17006-1701 (1996).

Bennett et al., "Cloning of a human UDP-N-acetyl-alpha-D-Galactosamine:polypeptide N-acetylgalactosaminyltransferase that complements other GalNAc-transferases in complete O-glycosylation of the MUC1 tandem repeat", *J Biol Chem*, 273:30472-30481 (1998).

Blixt et al., "Printed covalent glycan array for ligand profiling of diverse glycan binding proteins", *Proc Natl Acad Sci.*, 101(49):17033-17038 (Nov. 24, 2004).

Brandlein et al., "CFR-1 receptor as target for tumor-specific apoptosis induced by the natural human monoclonal antibody PAM-1", *Oncol Rep* 11:777-784. (2004b).

Cote et al., "Generation of human monoclonal antibodies reactive with cellular antigens", *Immunology: PNAS. USA.*, 80(7):2026-2030 (Apr. 1, 1983).

Danielczyk et al., "PankoMab: a potent new generation anti-tumour MUC1 antibody", *Cancer Immunol Immunother*, 55:1337-1347. (2006).

Dian et al., "Evaluation of a novel anti-mucin 1 (MUC1) antibody (PankoMab) as a potential diagnostic tool in human ductal breast cancer; comparison with two established antibodies", *Onkologie*, 32:238-244. (2009).

Gahring et al., "Granzyme B proteolysis of a neuronal glutamate receptor generates an autoantigen and is modulated by glycosylation", *J Immunol*, 166:1433-1438. (2001).

Hanisch et al., "Monoclonal-Antibody Bw835 Defines a Site-Specific Thomsen-Friedenreich Disaccharide Linked to Threonine Within the Vtsa Motif of Muc1 Tandem Repeats", *Cancer Research*, 55:4036-4040(1995).

Hellstrom et al., "Anti-mesothelin antibodies and circulating mesothelin relate to the clinical state in ovarian cancer patients", *Cancer Epidemiol Biomarkers Prev*, 17:1520-1526. (2008).

Iwai et al., "Molecular cloning and characterization of a novel UDP-GlcNAc:GalNAc-peptide beta1,3-N-acetylglucosaminyltransferase (beta 3Gn-T6), an enzyme synthesizing the core 3 structure of O-glycans", *J Biol Chem*, 277:12802-12809. (2002).

Julenius et al., "Prediction, conservation analysis, and structural characterization of mammalian mucin-type O-glycosylation sites", *Glycobiology*, 15:153-164. (2005).

Kawabata et al., "Antibody response against NY-ESO-1 in CHP-NY-ESO-1 vaccinated patients", *Int J Cancer*, 120:2178-2184. (2007).

Li et al., "Where do we place PankoMab in the reagents used to study the MUC1 superfamily?", *Onkologie*, 32:235-237 (2009).

Liu et al., "Proteomics-based identification of autoantibody against CDC25B as a novel serum marker in esophageal squamous cell carcinoma", *Biochem Biophys Res Commun*, 375:440-445. (2008).

Lu et al., "Humoral immunity directed against tumor-associated antigens as potential biomarkers for the early diagnosis of cancer", *J Proteome Res*, 7:1388-1394(2007).

Lubin et al., "Analysis of p53 antibodies in patients with various cancers define B-cell epitopes of human p53: distribution on primary structure and exposure on protein surface", *Cancer Res*, 53:5872-5876.(1993).

Pereira-Faca et al., "Identification of 14-3-3 theta as an antigen that induces a humoral response in lung cancer", *Cancer Res*, 67:12000-12006. (2007).

(Continued)

*Primary Examiner* — Laura B Goddard

(74) *Attorney, Agent, or Firm* — Ascenda Law Group, PC; Adda C. Gogoris

(57) **ABSTRACT**

Methods for identifying glycopeptides and more particularly glycopeptide epitopes that are specifically recognized by disease-associated auto-antibodies are provided. In some aspects the auto-antibodies are cancer-associated or autoimmune disease associated. In other aspects, methods of diagnosing a patient with cancer or an autoimmune disease, or for eliciting an immune response in a mammalian host directed to the glycopeptides of the invention are provided.

**3 Claims, 8 Drawing Sheets**

(56)

**References Cited**

OTHER PUBLICATIONS

Rauschert et al., A new tumor-specific variant of GRP78 as target for antibody-based therapy, *Lab Invest*, 88:375-386 (2008).

Reis et al., Development and characterization of an antibody directed to an alpha-N-acetyl-D-galactosamine glycosylated MUC2 peptide, *Glycoconj, J* 15:51-62. (1998).

Sabbatini et al., Pilot study of a heptavalent vaccine-keyhole limpet hemocyanin conjugate plus QS21 in patients with epithelial ovarian, fallopian tube, or peritoneal cancer, *Clin Cancer Res*, 13:4170-4177. (2007).

Sahin et al., "Human neoplasms elicit multiple specific immune responses in the autologous host.", *Immunology: PNAS USA*, 92(23) :11810-11813 (Dec. 5, 1995).

Snijdewint et al., Cellular and humoral immune responses to MUC1 mucin and tandem-repeat peptides in ovarian cancer patients and controls, *Cancer Immunology Immunotherapy*, 48:47-55 (1999).

Sorensen et al., Chemoenzymatically synthesized multimeric Tn/STn MUC1 glycopeptides elicit cancer-specific anti-MUC1 antibody responses and override tolerance. *Glycobiology*, 16:96-107 (2006).

Takeuchi et al., The epitope recognized by the unique anti-MUC1 monoclonal antibody MY.1E12 involves sialyl alpha 2-3galactosyl beta 1-3N-acetylgalactosaminide linked to a distinct threonine residue in the MUC1 tandem repeat, *Journal of Immunological Methods*, 270:199-209 (2002).

Tarp et al., Identification of a novel cancer-specific immunodominant glycopeptide epitope in the MUC1 tandem repeat, *Glycobiology*, 17:197-209. (2007).

Tarp et al., Mucin-type O-glycosylation and its potential use in drug and vaccine development, *Biochim Biophys Acta*, 1780:546-563 (2008).

White et al., Purification and cDNA cloning of a human UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase. *J Biol Chem* 270:24156-24165. (1995).

\* cited by examiner

FIG. 1

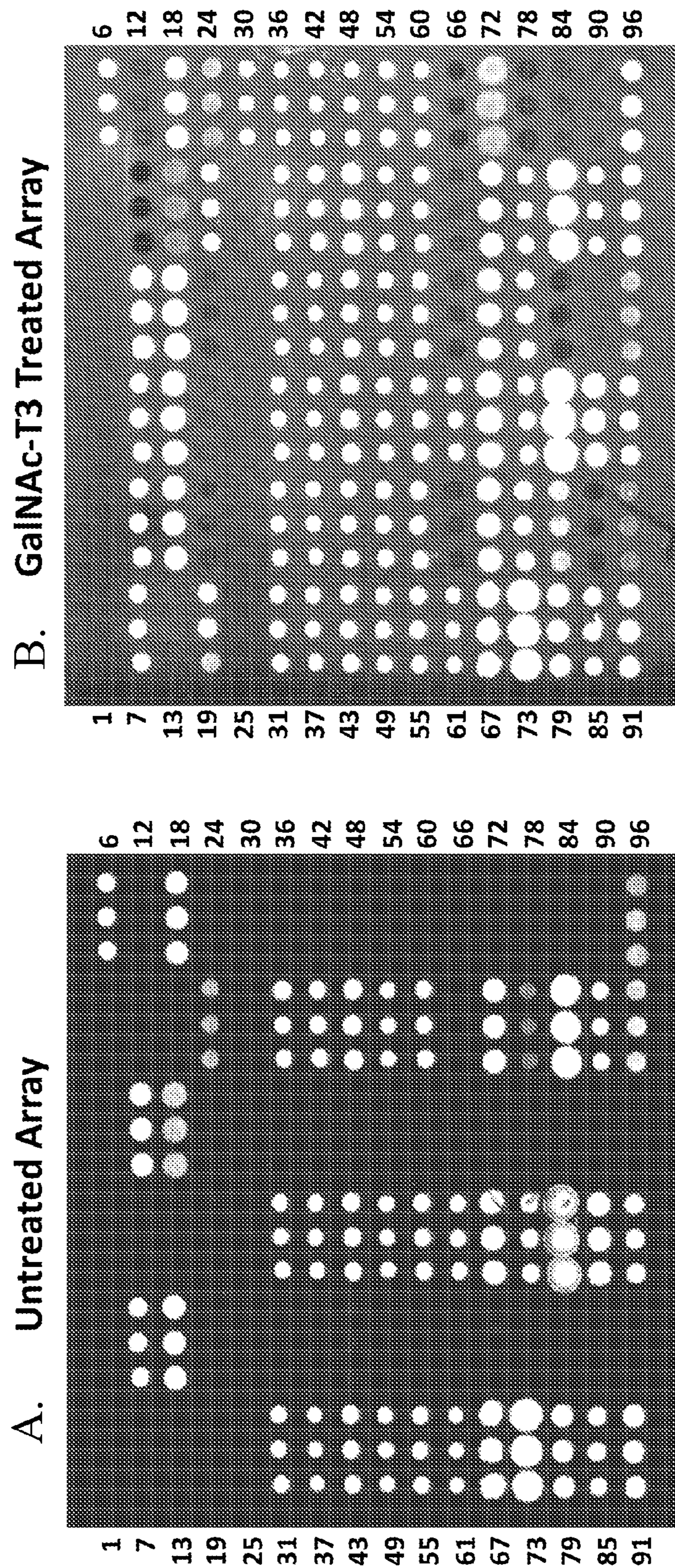
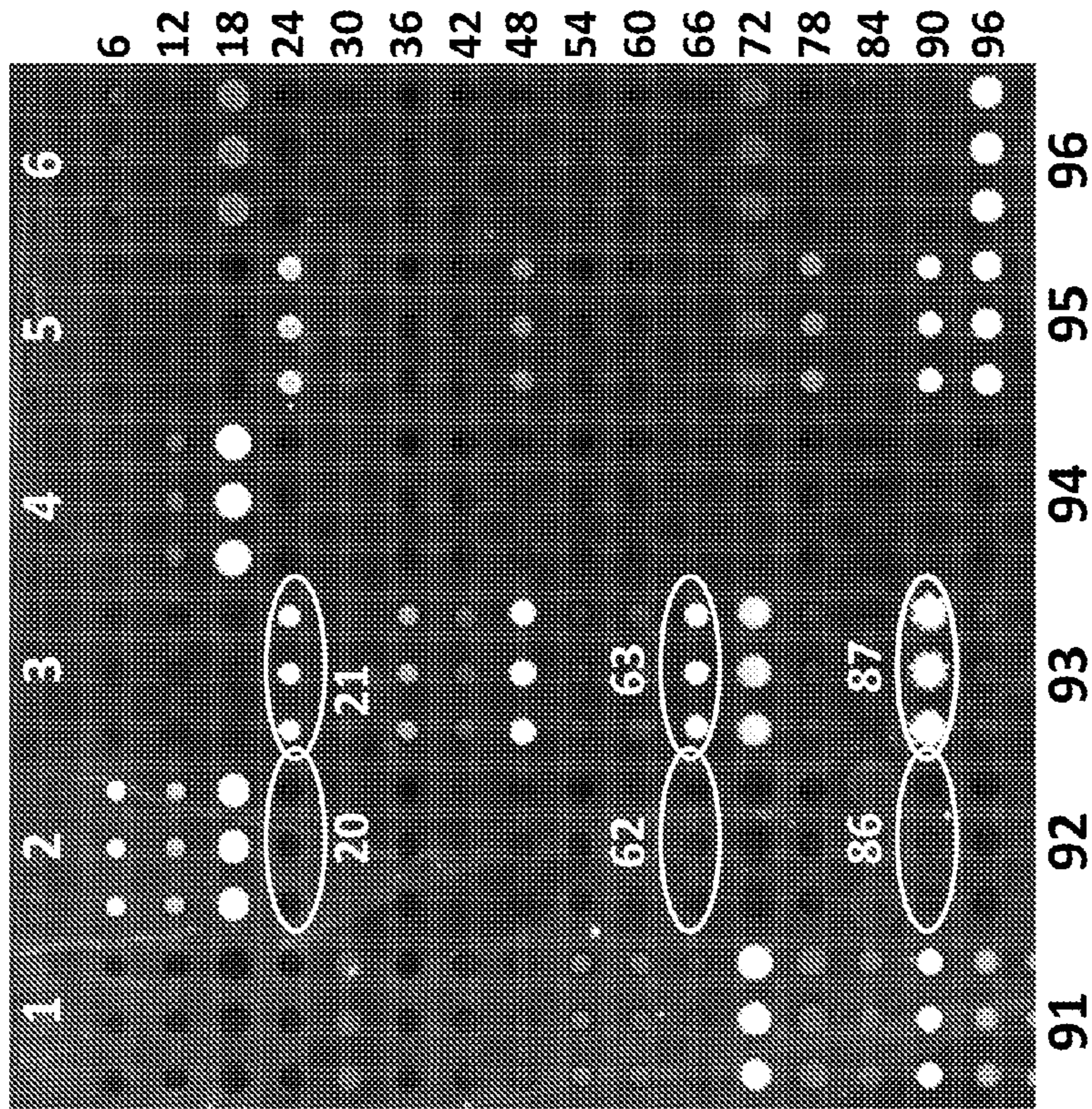


FIG. 2

A. Prostate Cancer Serum #762



B. Normal Serum #174

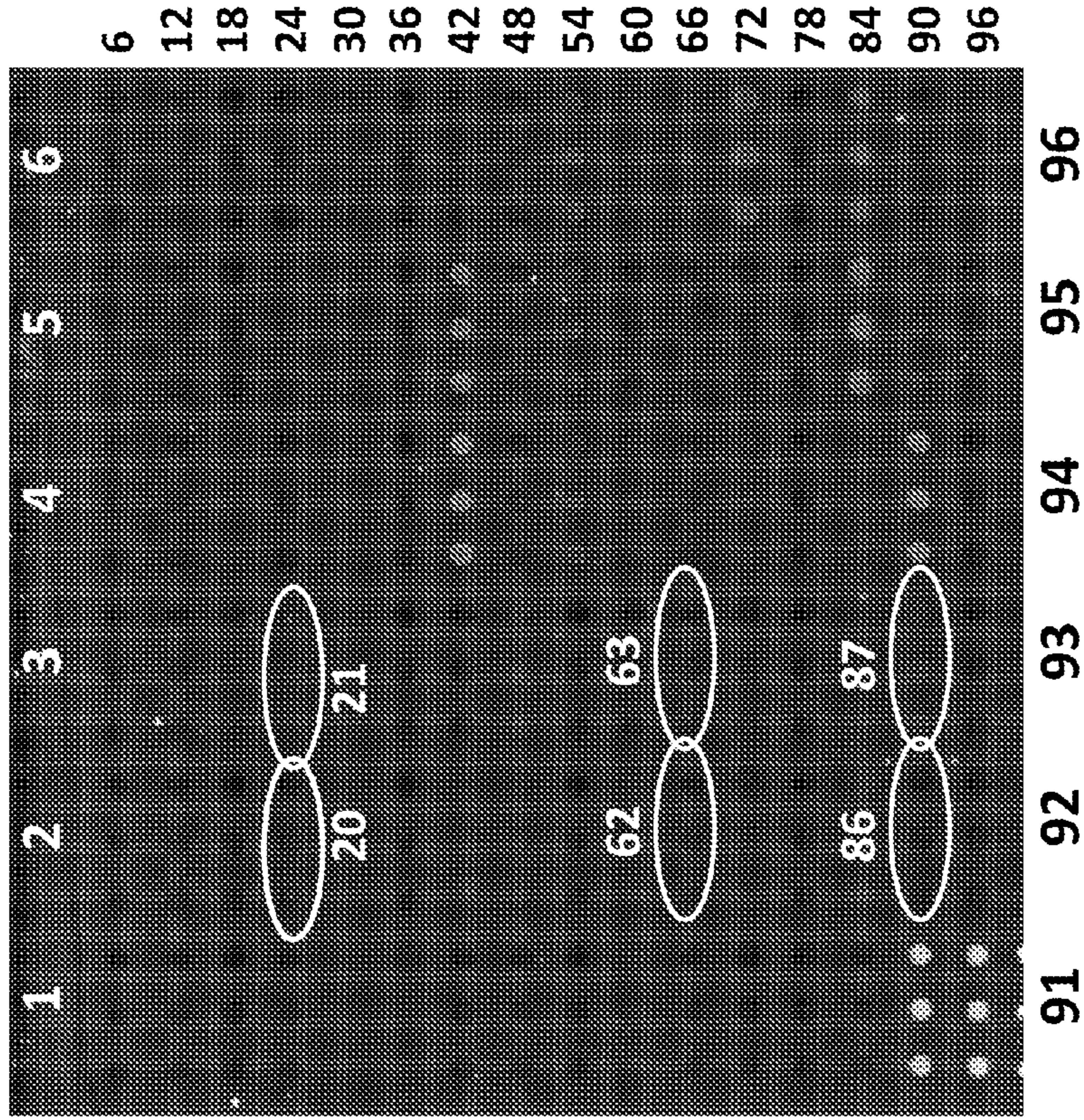


FIG. 3

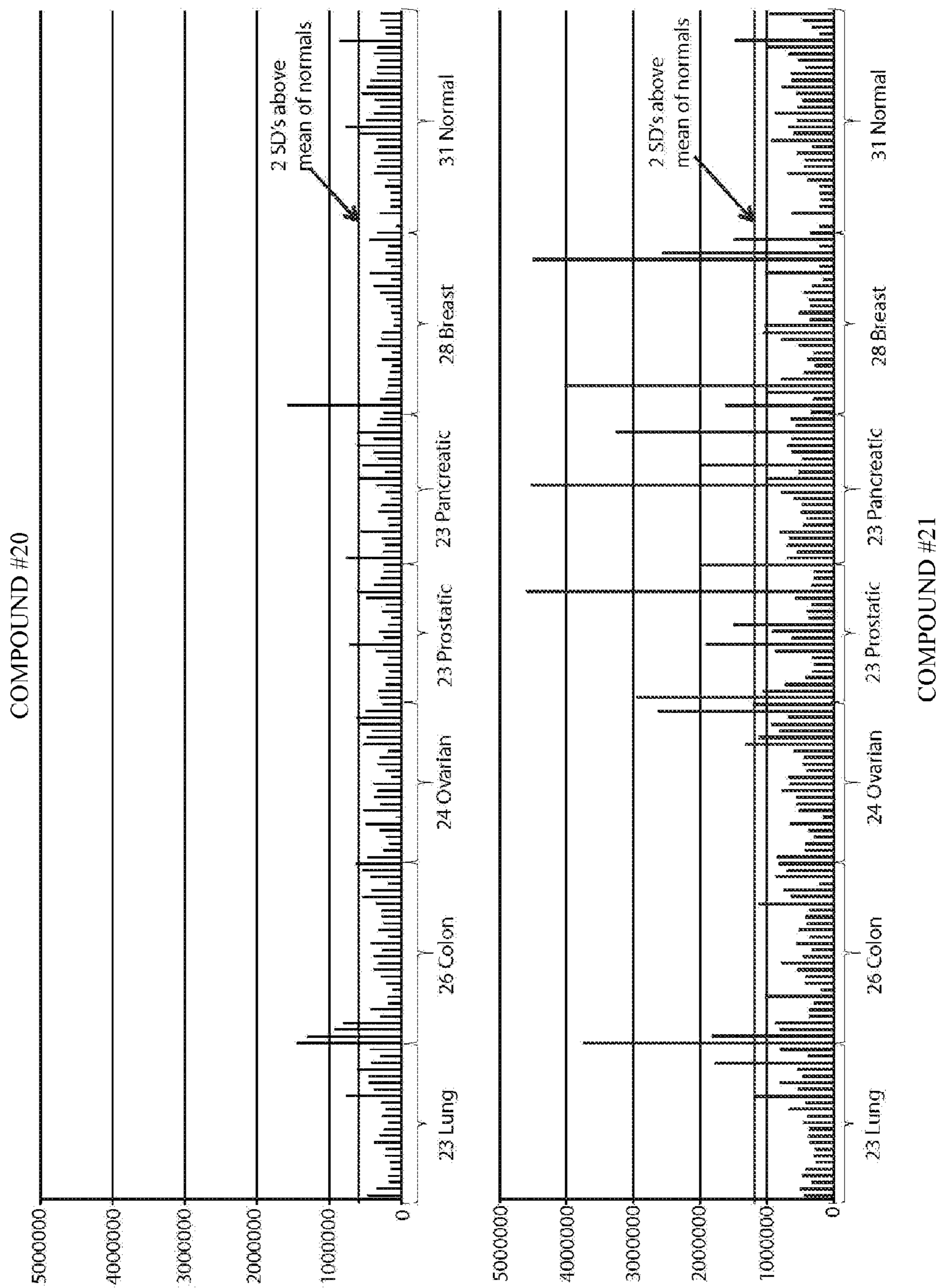
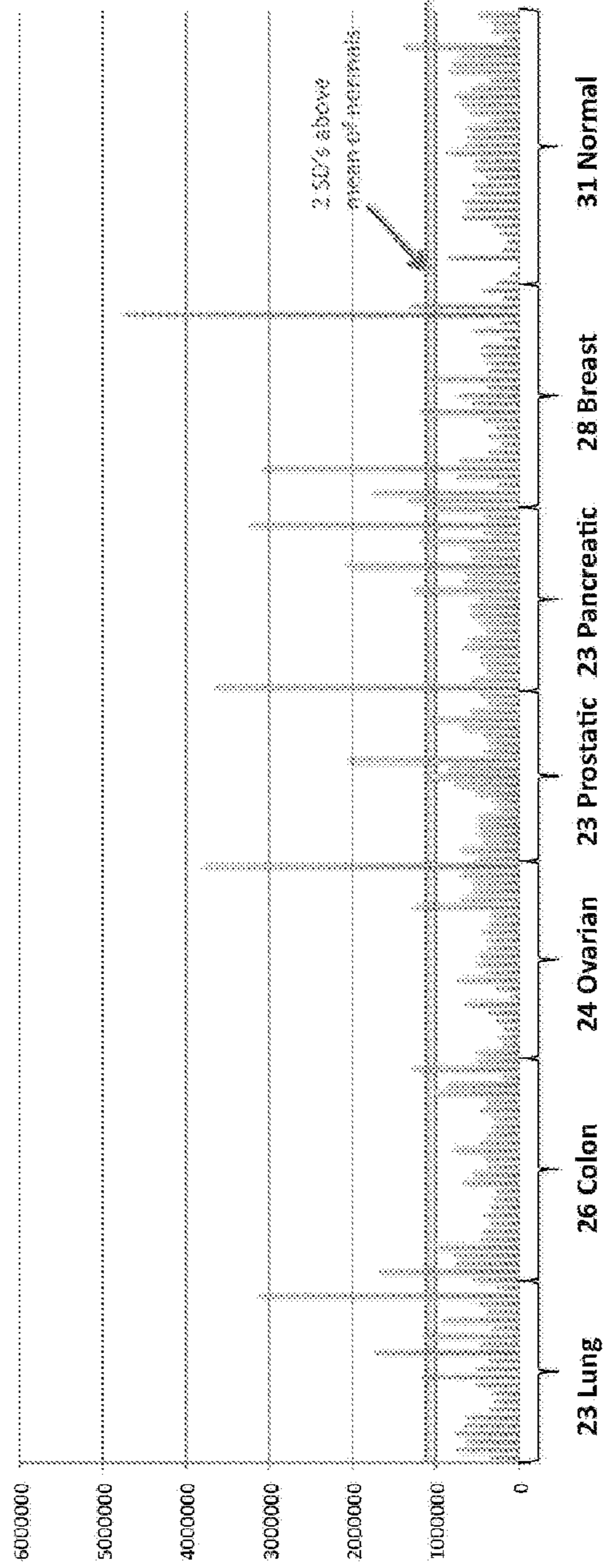
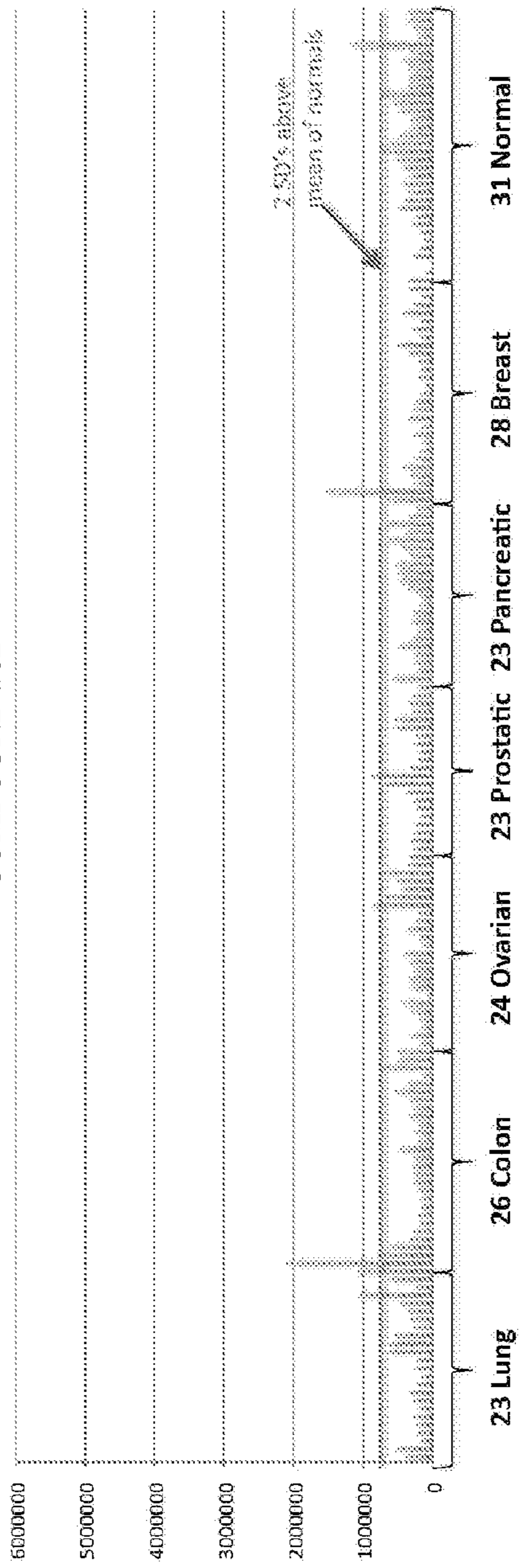


FIG. 4

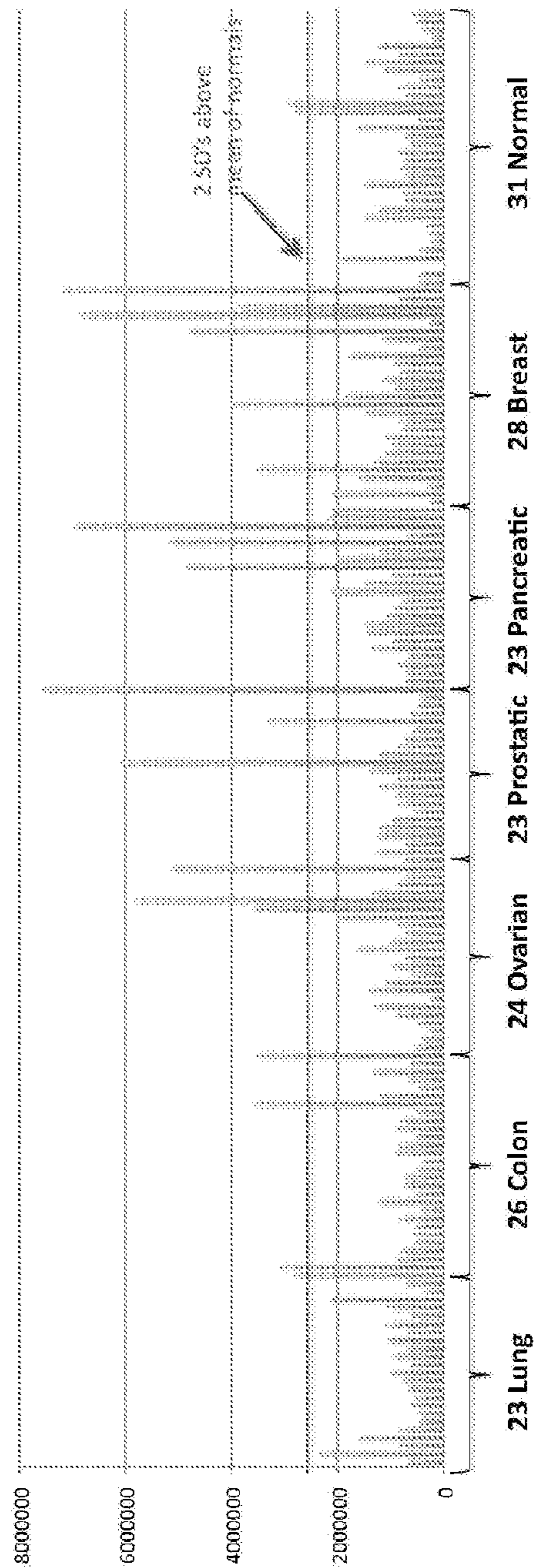
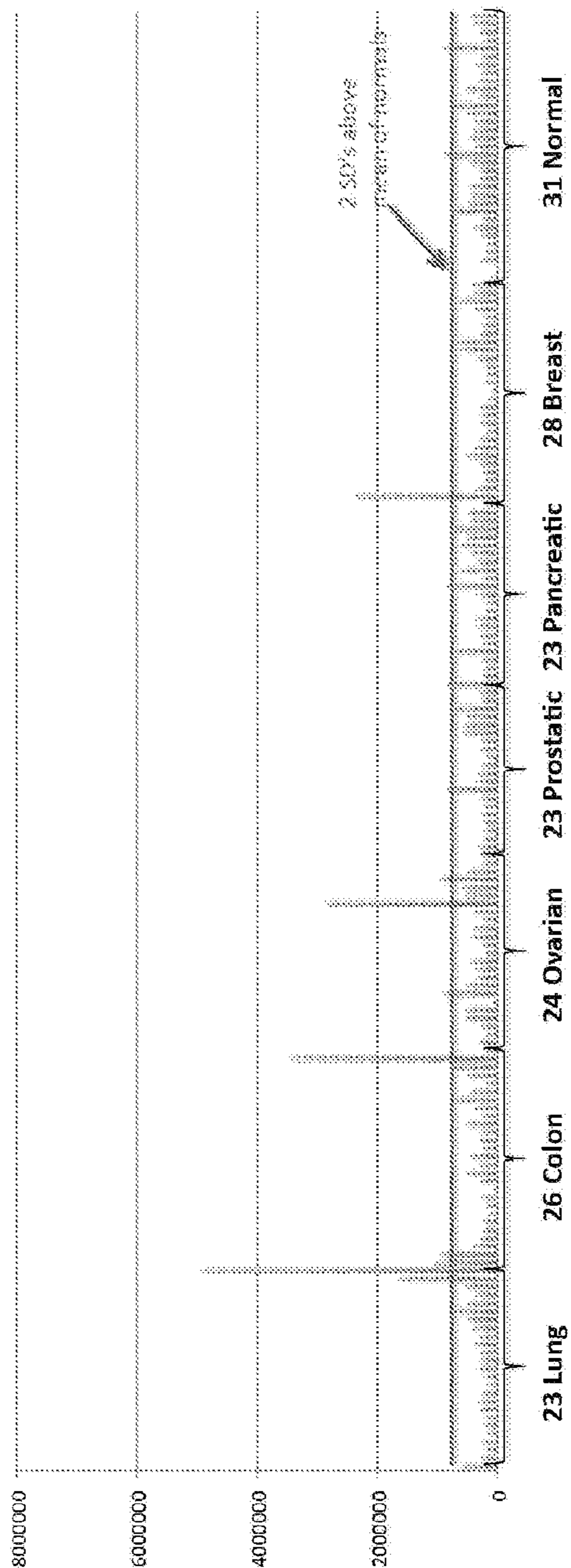
COMPOUND #62



COMPOUND #63

FIG. 5

COMPOUND #86



COMPOUND #87

FIG. 6A

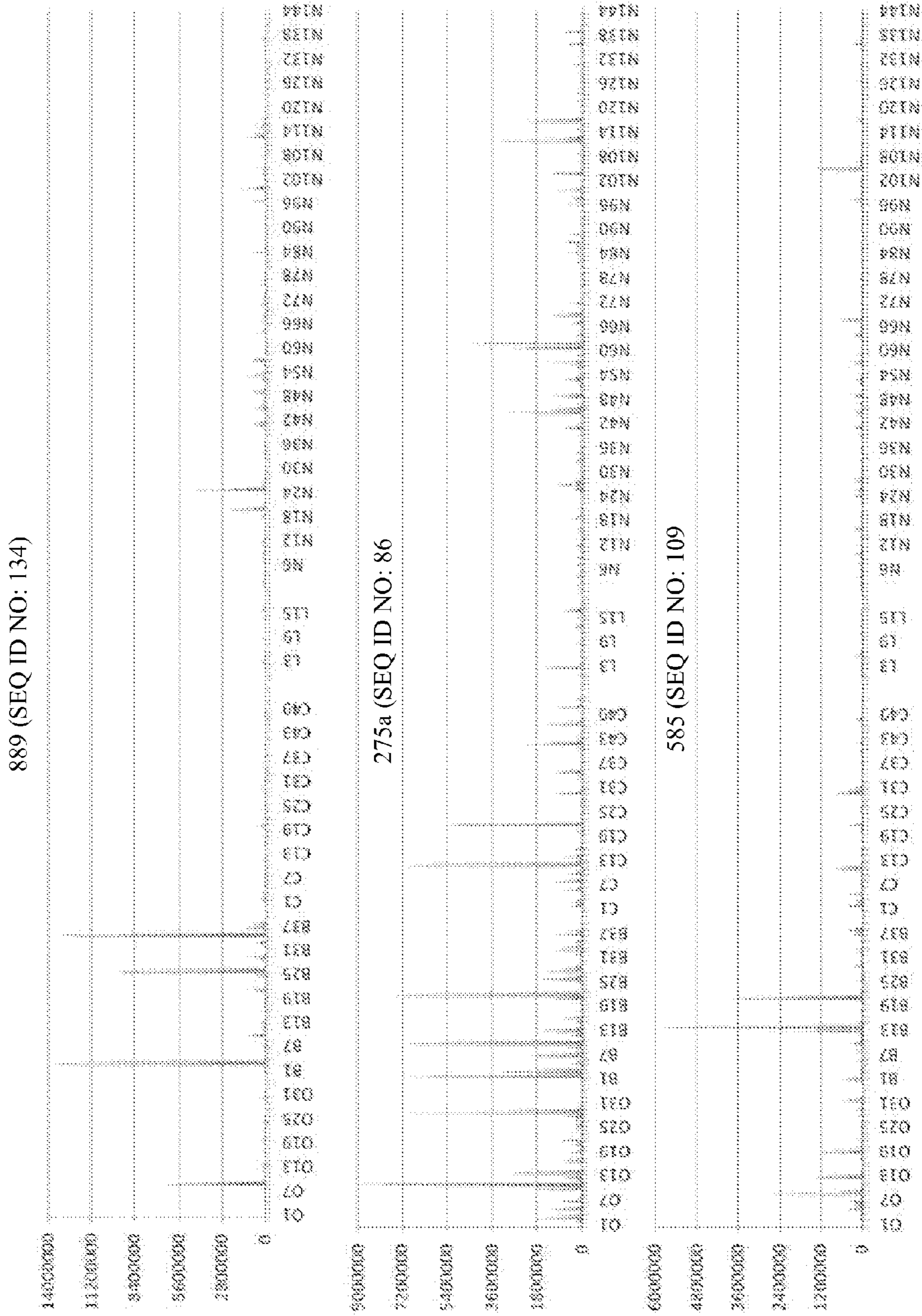
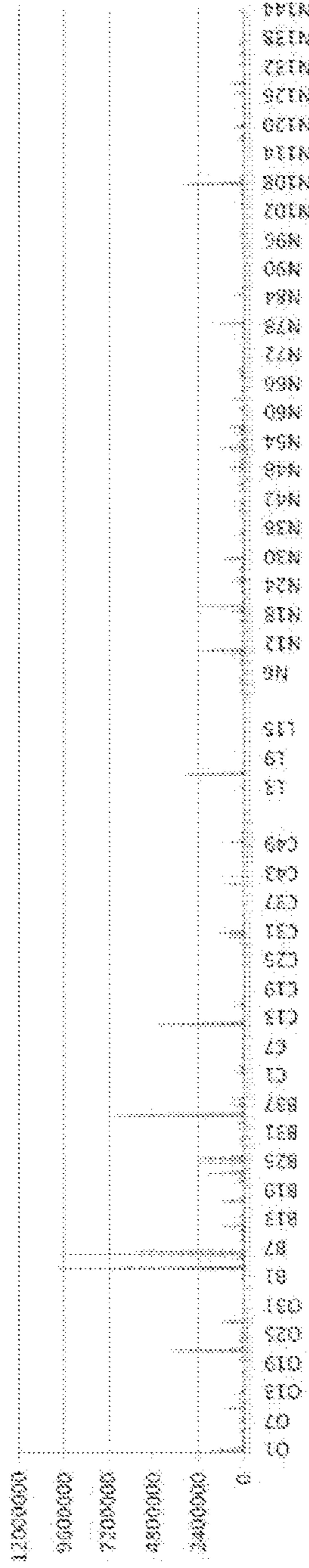


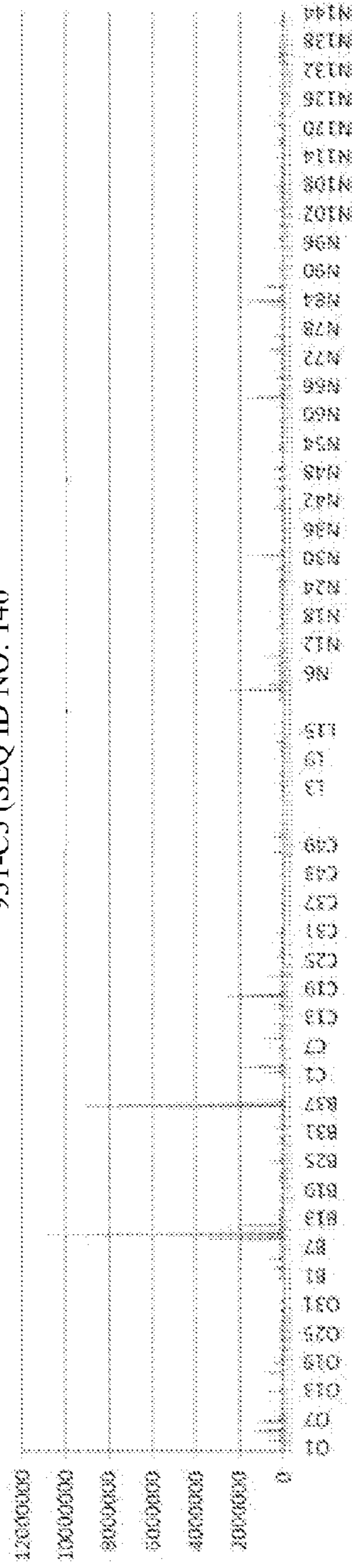


FIG. 6B

893 (SEQ ID NO: 135)



931-C3 (SEQ ID NO: 146)



852-C3 (SEQ ID NO: 145)

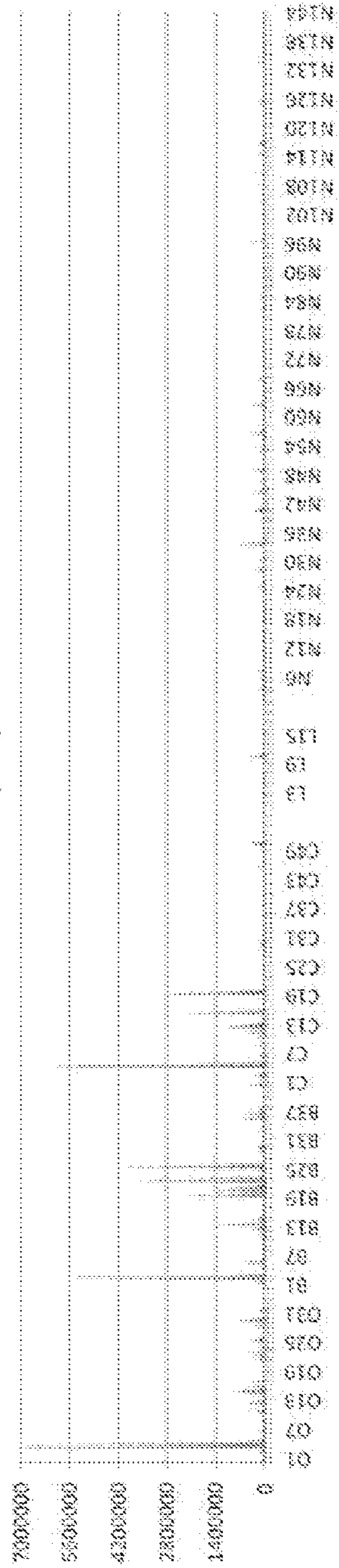
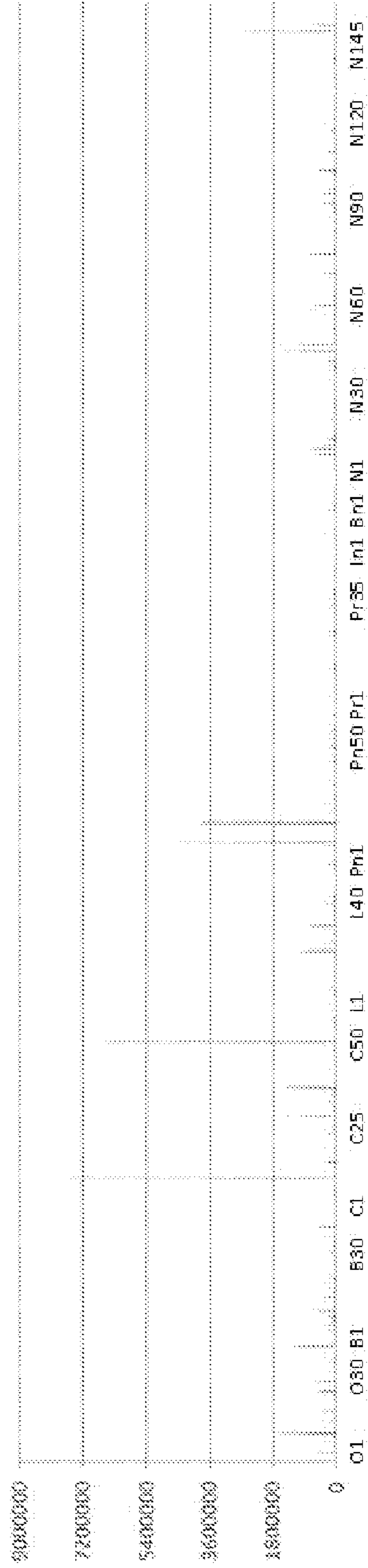
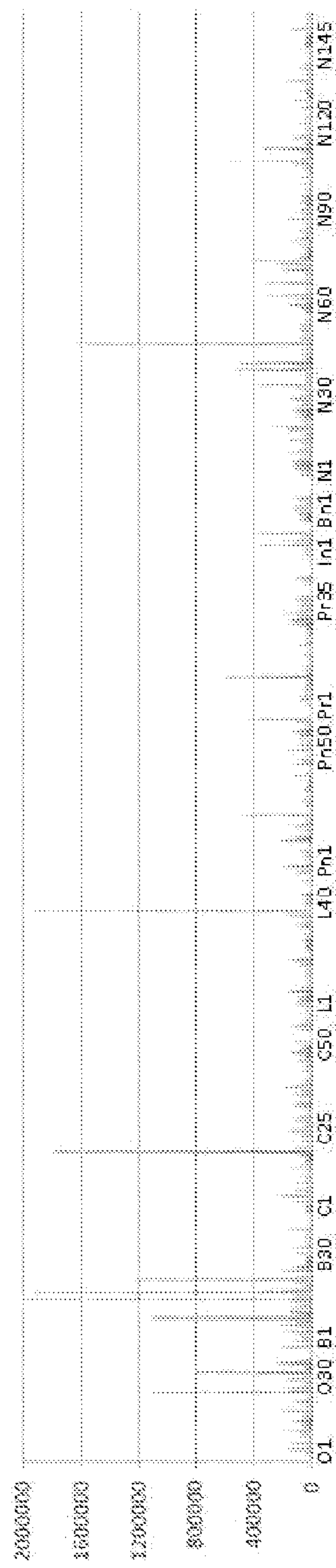


FIG. 6C

873 (SEQ ID NO: 132)



690 (SEQ ID NO: 116)



1

**METHODS OF IDENTIFYING  
GLYCOPEPTIDES RECOGNIZED BY  
DISEASE-ASSOCIATED AUTO-ANTIBODIES**

CROSS REFERENCE TO PRIOR APPLICATION

This application claims the benefit of U.S. Provisional Application Ser. No. 61/293,583 filed Jan. 8, 2010 and 61/294,477 filed Jan. 12, 2010, both of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention is related to methods for identifying glycopeptides and more particularly glycopeptide epitopes that are specifically recognized by disease-associated auto-antibodies. In some aspects the auto-antibodies are cancer-associated or autoimmune disease-associated. The invention also relates to methods of diagnosing a patient with cancer or an autoimmune disease, or for eliciting an immune response in a mammalian host directed to a glycopeptide of the invention. The invention also relates to novel individual glycopeptides as well as to panels of glycopeptides (whether individually novel or not) useful for autoantibody detection purposes.

BACKGROUND OF INVENTION

Malignant transformation of cells is virtually always accompanied by alterations in the posttranslational modifications (PTMs) of proteins, and one of the best documented examples is the abundant mucin-type O-glycosylation (hereafter referred to as O-glycosylation) found on mucins and other O-glycoproteins (Tarp and Clausen 2008). Tumor-associated changes in expression of O-glycoproteins and/or in their aberrant glycosylation, create a diverse set of unusual molecular structures found on the surface of cancer cells as well as in secretions. These molecular structures generally represent glycoproteins with truncated immature O-glycans, to which the immune system of man is not normally exposed except, in some cases, as biosynthetic intermediates and then only in the secretory pathway. Therefore, these structures may represent a different form of tumor-associated antigens (one not necessarily based on differential expression level or sequence mutation), to which individuals lack immunological tolerance and thus provoke both auto-antibodies and cell mediated immunity (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001).

Several mouse antibodies have been isolated and characterized as having unique binding specificity for combined glycopeptide epitopes that include both the peptide sequence as well as the aberrant PTM (hereinafter "APT<sup>M</sup>") for efficient binding. Examples include monoclonal antibodies that specifically recognize distinct O-glycopeptides from MUC2, MUC1, and other glycoproteins (Reis et al. 1998; Sorensen et al. 2006; Danielczyk et al. 2006; Dian et al. 2009; Li et al. 2009; Takeuchi et al. 2002; Clark et al. 1998).

There exist examples of human antibodies with selective or specific reactivity with PTM-modified proteins, but these are generally limited to inflammatory and autoimmune diseases (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001). Furthermore, human hybridoma technologies have identified natural IgM antibodies that react with glycoforms of proteins but the nature of the epitopes has not been fully clarified (Rauschert et al. 2008; Vollmers and Brandlein 2009; Brandlein et al. 2004a; Brandlein et al. 2004b; Rasmussen and Ditzel 2009). A major drawback of current technologies to screen for auto-antibodies directed

2

against APT<sup>M</sup> proteins is the lack of high through-put methods for identifying antigens, more particularly epitopes, for generating pertinent antigens and for screening such antigens.

In principle, cancer-associated auto-antibodies represent appealing potential biomarkers. Auto-antibodies may develop early in carcinogenesis, at the time tumor-associated antigens appear on premalignant or malignant lesions. Antibody responses can produce relatively high concentrations in circulation with a long circulation time, and they can be detected with sensitive and specific methods (see, (Lu et al. 2008; Anderson and Labaer 2005)). In contrast, antigens produced by small premalignant or malignant lesions are generally produced in vanishingly small levels that due to dilution and clearance from blood may not be detectable by conventional techniques. Discovery and characterization of specific auto-antibodies to cancer antigens have been undertaken using different approaches in the past. Classical studies identified such antibodies reactive with tumor cells, tissues, or isolated proteins (Kawabata et al. 2007), but distinct molecular features of binding epitopes have generally not resulted from these approaches.

More recent proteome-wide screening techniques have included expressed cDNA libraries (SEREX) (Sahin et al. 1995), protein and peptide arrays (Stockert et al. 1998; Pereira-Faca et al. 2007), random or designed phage displays (Mintz et al. 2003), and more recently self-assembling protein arrays (Ramachandran et al. 2008; Anderson et al. 2008). Cancer-associated auto-antibodies characterized to date have been found to bind intracellular proteins with functions important in cell cycle regulation, such as GPR78 (Mintz et al. 2003), p53 (Lubin et al. 1993), NY-ESO-1, and CDC25 (Liu et al. 2008), but also some cell membrane glycoproteins such as MUC1 (Snijdewint et al. 1999), HER2 (Chapman et al. 2007) and Mesothelin (Hellstrom et al. 2008).

Auto-antibodies are believed to be induced as a result of altered expression of proteins and altered molecular structure due to mutations, alternative splicing and post-translational events such as protein processing and aberrant enzymatic modifications including glycosylation (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001). These events induce breakage of tolerance and immunity may result. Surprisingly, however, few disease- or more specifically cancer-associated auto-antibody epitopes have been identified and molecularly defined despite considerable efforts and broad proteome screening. This is due to limitations in methods for identification of such auto-antibodies, in that, before the present invention, the appropriate antigen epitopes have not been determined and hence not tested to lead to identification of disease-associated antibodies, to serve as substrates for the detection of disease or to serve as prototype vaccines for induction of immunity against the epitopes of these autoantibodies.

There are few known examples of disease-associated human antibodies to proteins involving glycosylation. One important example is an immunodominant epitope in type II collagen comprising a glycosylated hydroxylysine residue that is involved in collagen-induced arthritis (Backlund et al. 2002). Glycosylation may also modulate protein processing and hence affect exposure of new epitopes as shown in Rasmussen's encephalitis, where an N-glycan blocks proteolysis of a neuronal glutamate receptor and a short preceding peptide epitope (Gahring et al. 2001). Several human monoclonal antibodies have been shown to be directed to epitopes affected by glycosylation (Rauschert et al. 2008; Vollmers and Brandlein 2009; Brandlein et al. 2004a; Brandlein et al.

2004b; Rasmussen and Ditzel 2009), but the nature of the molecular epitopes remains undefined.

There is therefore a need to develop methods for the identification of PTM-containing peptides, such as aberrant glycopeptides (hereinafter "AGP"), that are specifically recognized by disease-associated auto-antibodies. The present invention provides such methods. There is also a need for improved diagnostic tools, such as AGP, that would permit early detection of disease, notably cancer, for example by being used as substrates to capture disease-associated autoantibodies.

#### SUMMARY OF INVENTION

In one embodiment, the invention provides a method for identifying glycopeptides reactive with cancer-associated auto-antibodies, the method comprising: providing a panel comprising peptides, at least a plurality of the peptides comprising one or more sites amenable to glycosylation, wherein at least one of the glycosylation sites has been modified with a glycan to form a glycopeptide having a peptide portion and a glycan portion; contacting the panel with an antibody-containing sample from a patient with cancer; and identifying glycopeptides in the panel that (i) are selectively recognized by antibodies in the sample, but not by antibodies in a control sample and (ii) are recognized by such antibodies in the sample through recognition of both the peptide portion and the glycan portion and not through recognition of either the peptide or the glycan alone.

In another embodiment, a panel of the invention comprises a plurality of peptides having an amino acid sequence comprising at least one serine or threonine residue, wherein the residue is a glycosylation site. In yet another embodiment, the at least one serine or threonine residue is at about the middle of the amino acid sequence. In still another embodiment, a panel of the invention comprises mutants of the peptides. The number of peptides in a panel may vary and may be at least 8 peptides, for example between about 8 and about 30 peptides, such as 10, 12, 15 or 20 peptides. A number of peptides in excess of 30 is also within the invention. The upper limit of peptides in a panel is limited by practical considerations (e.g., how many peptides can fit on a substrate) or cost-benefit considerations. Preferably the peptides are selected from the group consisting of SEQ ID NOs 15, 36, 49, and 82-146.

In a specific aspect of the above embodiment, providing a method for identifying glycopeptides reactive with cancer-associated auto-antibodies, the method further comprises identifying cancer-associated glycopeptide epitopes. In another aspect, the method further comprising elucidating the epitope structure of the identified glycopeptide epitopes.

In a specific embodiment, the invention provides a method for determining whether a patient has cancer, the method comprising: contacting an antibody-containing sample from the patient with a panel comprising peptides at least a plurality of which are glycopeptides, each glycopeptide comprising a glycopeptide epitope, the epitope having been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of the panel when not glycosylated; nor (b) the corresponding glycan when not bound to the peptide; and (ii) not to be recognized by antibodies in control sera; contacting the panel with an antibody-containing sample from the patient; determining if antibodies in the sample are bound to glycopeptides of the panel; and concluding either that the patient has cancer if the sample comprises antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have

cancer if the sample does not comprise antibodies that bind to at least one glycopeptide in the panel.

In one aspect of the above embodiment providing a method for determining whether a patient has cancer, the patient is newly diagnosed with cancer. In another aspect, the method further comprises concluding either that the patient has cancer if the sample comprises IgG antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have cancer if the sample does not comprise IgG antibodies that bind to at least one glycopeptide in the panel. In yet another aspect, the patient is diagnosed with cancer if said sample comprises antibodies that specifically recognize one or more of the glycopeptides having an amino acid sequence selected from the group consisting of: SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146).

In another embodiment, the invention provides a method for eliciting an immune response in a patient, the method comprising administering to the patient a composition comprising (i) a glycopeptide consisting essentially of an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPPSI (SEQ ID NO: 146), in an effective amount for eliciting the immune response; and (ii) a suitable adjuvant.

In a specific aspect of the above embodiment, providing a method for eliciting an immune response in a patient, the immune response comprises an IgG antibody response. In another aspect, the immune response is an anti-cancer immune response. In yet another aspect, the cancer is selected from the group consisting of breast cancer; colon cancer; ovarian cancer; cervical cancer; pancreatic cancer; prostatic cancer; liver cancer; kidney cancer; brain cancer; hematological cancer; testis cancer; head and neck cancer; and lung cancer.

In one aspect of the above embodiment, providing a method for eliciting an immune response in a patient, the glycopeptide is modified with an O-glycan at at least one amino acid residue. In another aspect, the at least one amino acid residue is a serine or threonine residue.

In any of the above embodiments of the invention, each of the peptides in the panel may be about 2 to about 50 amino acid residues in length. In other aspects, each of the peptides in the panel may be about 4 to about 25 amino acid residues in length.

In certain aspects of the above embodiments of the invention, the amino acid sequence of the peptides of the panel is a fragment found in a protein or variant of said protein or a conservative mutant. In some of the above embodiments, the identified glycopeptides of the panel are found in at least one glycoprotein that is aberrantly glycosylated in cancer cells. In

yet other of the above embodiments, glycopeptides identified by the methods of the present invention are found in at least one glycoprotein that is overexpressed in cancer cells.

In other aspects, the glycopeptides are synthesized synthetically or chemoenzymatically. In still other of the above aspects, the glycopeptides of the panel are partially glycosylated peptides when immobilized on the panel.

In certain of the above embodiments, the control sample contains pooled samples from a plurality of control individuals.

In certain of the above aspects of the invention, the panel is a microarray slide. In other aspects, the glycopeptides identified by the methods of the invention are selectively recognized by an IgG antibody. In certain of the above embodiments, the panel comprises one or more glycopeptides having an amino acid sequence selected from the group consisting of: SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPSI (SEQ ID NO: 146).

In another aspect, the invention provides a glycopeptide comprising an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPSI (SEQ ID NO: 146).

In yet another aspect, the invention provides a glycopeptide consisting essentially of an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPSI (SEQ ID NO: 146).

In still another aspect, the invention provides a glycopeptide consisting of an amino acid sequence selected from the group consisting of SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPSI (SEQ ID NO: 146).

In another aspect, the invention provides a pharmaceutical composition comprising one or more glycopeptides selected from the group consisting of SEQ ID NOs 15, 36, 49, and 82-146. Preferably, the pharmaceutical composition comprises one or more glycopeptides selected from the group consisting of LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPSI (SEQ ID NO: 146).

In yet another aspect, the invention provides for a panel of glycopeptides comprising at least a plurality of glycopeptides, each glycopeptide comprising a glycopeptide epitope, said epitope having been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera, said plurality comprising at least 8 glycopeptides selected from the group consisting of glycopeptides having SEQ IDs 15, 36, 49, and 82-146. Preferably, the plurality of glycopeptides comprises SHHSDESDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQNSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTRPALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQATDTFSTVPPTPSI (SEQ ID NO: 146).

In any of the above embodiments of the invention, the glycopeptides of the panel may be glycosylated in situ, in solution, or in vivo by recombinant expression in a host cell. In any of the above embodiments, the glycopeptides of the panel may be treated with one or more exoglycosidases to expose O-glycans. In still other of the above embodiments, the glycan may be an O-glycan. In any of the above embodiments, the O-glycan may be a member selected from the group consisting of: Tn, STn, T, Truncated C3, Truncated C2, Truncated C4, non-capped type1-C3, non-capped type2-C2, non-capped type2-C4, GalNAca-Tn, SA-type1-C3, SLea-C3, LacDiNAc-C3, LacDiNAc-C2, and LacDiNAc-C4.

In certain of the above embodiments, at least one glycopeptide in the panel is not a glycopeptide comprising a glycosylated GSTA motif.

In certain of the above embodiments, none of the glycopeptides in the panel are glycopeptides comprising a glycosylated GSTA motif.

These and other aspects of the present invention will be apparent to those of ordinary skill in the art in light of the present specification, claims and drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an image of a microarray slide and illustrates an example of on-slide (in vitro) glycosylation with a polypeptide GalNAc-transferase, GalNAc-T3, to glycosylate peptides and GalNAc glycopeptides with additional unsubstituted Ser/Thr residues to enhance number of O-glycans. FIG. 1A: GalNAc-T3 untreated array, FIG. 1B: GalNAc-T3 treated array.

FIG. 2 is an image of a microarray slide and illustrates reactivities of serum (1:25 dilution) from a newly diagnosed prostate cancer patient (#762 in FIG. 2A) and a normal control serum from an individual that does not have prostate cancer (#174 in FIG. 2B) on the library of 96 paired peptides/ GalNAc-glycopeptides as designated in Table II.

FIGS. 3-5 are bar graphs and illustrate microarray screening results from 147 cancer and 31 control sera on the glycopeptide pairs identified herein as #20/21 (FIG. 3), #62/63 (FIG. 4), or #86/87 (FIG. 5).

FIG. 6 are bar graphs showing 8 selected glycopeptides (i.e., 889, 275a, 585, 893, 931-C3, 852-C3, 873, and 690) reactive with IgG from newly diagnosed cancer patients compared to normal control sera. FIG. 6A: glycopeptides 889 (SEQ ID NO: 134), 275a (SEQ ID NO: 86), and 585 (SEQ ID NO: 109). FIG. 6B: glycopeptides 893 (SEQ ID NO: 135), 931-C3 (SEQ ID NO: 146), and 852-C3 (SEQ ID NO: 145). FIG. 6C: glycopeptides 873 (SEQ ID NO: 132) and 690 (SEQ ID NO: 116). The following human sera were used for FIGS. 6A and 6B: 32 ovarian cancer (O), 38 breast cancer (B), 54 colon cancer (C), 17 lung cancer (L), as well as 145 normal sera (N) (Asterand Corp). The following sera were used for FIG. 6C: 32 ovarian cancer (O), 38 breast cancer (O), 54 colon cancer (C), 42 lung cancer (L), 52 pancreatic cancer (Pn), 35 prostatic cancer (Pr), 8 inflammatory disease (In), 8 benign controls (Bn), and 145 healthy controls (N). Sera were screened at 1:20 dilution. Anti-human-IgG conjugated to Cy3 was used as the secondary detection unit and slides were scanned with a GenePix 4200AL Microarray Scanner.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for identification of peptides and peptide epitopes that comprise one or more posttranslational modification(s) (PTM(s)) ("PTM-peptides"/"PTM peptide epitopes") that are selectively recognized and bound by human disease-associated antibodies. These will include peptides that display an aberrant glycosylation pattern either due to an alteration in sequence (mutation) which invites a changed glycosylation pattern, or simply a glycosylation pattern not normally encountered in cancer-free individuals. Such peptides will constitute AGP as the term is introduced and hence defined above. For the removal of doubt, PTM-epitopes are not whole molecules; therefore, any discussion of such epitopes should be construed as applying to glycopeptides harboring such epitopes.

In some aspects, the PTM-peptides of the invention are useful for diagnosing a disease. In a specific embodiment, the present invention provides methods for diagnosing a patient with cancer. In another embodiment, the patient is newly diagnosed with cancer (i.e., diagnosed with cancer for the first time). In still other embodiments, a patient is diagnosed with an autoimmune disease.

In certain embodiments, the methods are useful for identifying PTM-peptides that are useful for eliciting in an individual an immune response directed against PTM-epitopes that are associated with disease, such as cancer. In certain embodiments, the immune response includes an auto-antibody response. In certain aspects, the induction of auto-antibodies to aberrant PTM-modified glycoproteins includes antibodies that specifically recognize O-glycopeptide epitopes.

As discussed, supra, malignant transformation of cells is virtually always accompanied by alterations in the posttranslational modifications (PTMs) of proteins, including O-glycosylation (Tarp and Clausen 2008). Tumor-associated changes in expression of O-glycoproteins and/or in their aberrant

glycosylation, create a diverse set of unusual molecular structures found on the surface of cancer cells as well as in secretions. These molecular structures generally represent glycoproteins with truncated immature O-glycans, to which the immune system of man is not normally exposed except, in some cases, as biosynthetic intermediates and then only in the secretory pathway. Thus, one aspect of the PTM-peptides and PTM peptide epitopes identified by the methods of the present invention, i.e., AGP, is that they are not covered by immunological tolerance, and hence are potential targets for immunotherapeutic intervention. The aim of eliciting immune responses in a host using the AGP of the invention is the development of vaccines against the very disease that the AGP or other PTM-peptides are associated with.

Thus, AGP can cause induction of auto-antibodies to PTM-peptide epitopes. One aspect of this invention is the design and production of PTM-peptide libraries that represent or more accurately contain AGP associated with disease. In another aspect of the invention, high through-put methods for screening of disease-associated antibodies using such libraries are provided. In a specific embodiment, the invention relates to aberrant O-glycosylation of glycoproteins and more specifically, of glycopeptides. The present inventors believe one of the reasons why these disease-associated PTM-peptides and epitopes have eluded detection and especially association with disease is that the proteins bearing them in vivo are not or not necessarily mutated or overexpressed and hence would not be detected by ordinary, nontargeted, techniques.

PTM modifications can be the result of the addition of chemical groups to a protein, such as a phosphate group or a sugar moiety (e.g. acetylation of lysine and serine, glycosylation of asparagine, serine, threonine, hydroxyl-proline, lysine, methylation of arginine, histidine, and lysine, phosphorylation of serine, threonine, and tyrosine). They can also be the result of a conversion of an amino acid to a distinct structure, as in the deimination of arginine to citrulline or the deamidation of aspartic acid/asparagine to isoaspartic acid. While this invention is primarily concerned with glycosylation, it is evident that other aberrant posttranslational modifications as described herein may result in altered proteins harboring aberrant PTM-epitopes that may be the target of auto-immunity.

In some aspects of the present invention, the discriminating characteristic of the peptides and peptide epitopes useful in the present invention is that disease-associated antibodies bind selectively with the PTM-containing peptide and not with the same unmodified peptide or the PTM in the context of a different peptide sequence or another unrelated (e.g., artificial) carrier. In terms of AGP having diagnostic and/or immunogenic value, the disease-associated autoantibodies should recognize only the combination of the relevant glycosylated amino acid sequence and not the same glycan on a different peptide nor the same amino acid sequence bearing a different glycan. This will avoid false positives. It will be understood that the construction of peptide libraries and the availability of disease (e.g., cancer) and control sera that can be tested renders it unnecessary to know beforehand which AGP will be recognized by disease-associated antibodies in order to identify these antibodies. Once the disease-associated antibodies have been identified, they, or man-made versions thereof can be used to pinpoint the AGP that pulled relevant autoantibodies out of the sera.

In other aspects, the invention provides methods for the diagnosis of a patient with a disease, such as, e.g., cancer, wherein detection of antibodies in a sample from the patient that selectively recognize one or more combinations of disease-associated PTM-containing peptides is used to predict

and diagnose disease. In still other embodiments, methods for treating a patient with cancer using compositions or vaccines comprising PTM-containing peptides or proteins of the invention are provided.

#### DEFINITIONS

As used herein, the term “immune response” includes an adaptive immune response, including a T cell response and B cell response. Thus, as used herein, the term “eliciting an immune response” means that an adaptive immune response is induced by administration of an appropriate immunogen (antigen or antigen plus carrier).

As used herein, an “anti-cancer immune response” is an immune response that is directed toward cancer cells or products secreted or shed from cancer cells. For example, an anti-cancer immune response may be characterized by tumor-specific antibodies and/or cytotoxic T cells that attack cancer cells or react specifically with a glycoprotein shed from cancer cells.

An “auto-antibody” is an antibody that specifically recognizes an epitope harbored by a self-product such as a protein, carbohydrate or lipid produced by healthy or diseased cells of an individual.

As used herein, the terms “selective binding” and “selective recognition” and their grammatical variants, of an epitope by an antibody means that the antibody binds with significantly greater affinity to the epitope compared to any other sequence or structure.

The term “epitope” refers to the part of an antigen that is specifically recognized and bound by an antibody. The term “glycopeptide epitope” is an epitope that includes both part of a peptide sequence and at least part of a glycan. The term “minimal epitope” or “minimal glycopeptide epitope” refers to the shortest glycopeptide that is recognized by antibodies recognizing the same epitope.

As used herein, the term “corresponding peptide” refers to the unglycosylated form of a glycopeptide of the invention. Thus, a glycopeptide and its corresponding peptide have the same amino acid sequence.

The term “glycan hapten” refers to glycan moiety independent of whether this is conjugated to a carrier, such as a peptide or protein (i.e. binding to the glycan hapten does not depend on the carrier such as protein or peptide to which the glycan is bound).

The terms “linear peptide” and “linear peptide epitope” means that the peptide or peptide epitope is non-conformational (i.e., antibody recognition and binding to the epitope does not depend upon the three-dimensional structure of the peptide).

The term “disease-associated antibody” means an antibody that is detected in a patient sample if the patient has the disease, but is not detected, or is present at significantly reduced levels compared to the patient sample, in a control sample. For example, a cancer-associated antibody is present in an antibody-containing sample from a patient with cancer, but is not present, or is present at significantly reduced levels in a sample from a patient without cancer. A useful distinguishing range of antibody levels is at least two or preferably three fold higher levels in patients compared to healthy control. The term may also apply to groups of patients with a disease, where “disease-associated antibody” means an antibody that is detected with higher prevalence/incidence in the disease group compared to a healthy control group. A useful distinguishing prevalence (=specificity of assay) would be at least 70% and preferably 80 or 90%,

The term “aberrant glycosylation” means a glycoform that is not normally present on proteins expressed on the cell surface or secreted/shed from cells. An example of an aberrant glycoform is Tn (GalNAc $\alpha$ 1-O-Ser/Thr), sialosyl-Tn (NeuAc $\alpha$ 2-8GalNAc $\alpha$ 1-O-Ser/Thr), and T (Gal $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr).

As used herein, a “glycosylatable peptide” or a peptide containing a “site amenable to glycosylation” refers to a peptide containing an amino acid residue that can be glycosylated. An example of a site amenable to glycosylation is a peptide site containing a serine or threonine amino acid residue, which can be O-glycosylated with N-acetyl-galactosamine (GalNAc).

As used herein, “variant” in addition to its understood meaning as a term of art includes any changes in a molecule from its wild-type form. For example, alleles, fragments, mutations, substitutions with natural or analog compounds, splice variants, glycosylations, species variants, and the like. The term is not limited to any one type of change or deviation from the wild type form or “normal” molecule. A “variant” also includes a polypeptide or enzyme which has at least 60% amino acid identity as determined by BLAST or FASTA algorithms, preferably at least 75%, most preferably at least 85%, and even more preferably at least 90%, and still more preferably at least 95%, and which has the same or substantially similar properties or functions as the native or parent protein or enzyme to which it is compared.

“Conservative mutants” are those in which a given amino acid residue in a protein or enzyme has been changed without altering the overall conformation and function of the polypeptide, including, but not limited to, replacement of an amino acid with one having similar properties (such as, for example, polarity, hydrogen bonding potential, acidic, basic, hydrophobic, aromatic, and the like). Amino acids with similar properties are well known in the art. For example, arginine, histidine and lysine are hydrophilic-basic amino acids and may be interchangeable. Similarly, isoleucine, a hydrophobic amino acid, may be replaced with leucine, methionine or valine. Such changes are expected to have little or no effect on the apparent molecular weight or isoelectric point of the protein or polypeptide.

An “organ-specific glycoprotein” is a glycoprotein which is only or which has substantial preferential expressed in a specific organ type. For example, the protein mucin 16 (MUC16) (SEQ ID NO: 57), is only expressed in epithelium of the female tract such as ovary and endometrium, and it is primarily overexpressed in tumors originating from these epithelia.

The term “clinical debut” refers to the first time a patient is diagnosed with a disease.

The term “immunogenic substitution” means the replacement of an amino acid residue with a different amino acid that causes the antigen to become immunogenic. For example, a substitution of an amino acid in a self protein, such as that which can result from a cancer mutation, or experimentally in a peptide, that renders the self protein immunogenic (i.e., breaks immunogenic tolerance to the self protein) is an immunogenic substitution. As another example, the substitution of a normally unmodified amino acid with a modified amino acid, wherein the modification itself (i.e., as a hapten, such as, e.g., Tn) is immunogenic, can render a protein immunogenic.

The term “subject” or “individual” as used herein refers to an animal having an immune system, preferably a mammal (e.g., rodent, such as mouse). In particular, the term encompasses humans.

As used herein, the term “about” or “approximately” usually means within an acceptable error range for the type of value and method of measurement. For example, it can mean within 20%, more preferably within 10%, and most preferably still within 5% of a given value or range. Alternatively, especially in biological systems, the term “about” means within about a log (i.e., an order of magnitude) preferably within a factor of two of a given value.

As used herein, the term “consisting essentially of” means that the glycopeptide sequence is not limited to a length of 20 amino acids, but can be longer or shorter. For example, a glycopeptide can be less than or more than 20 amino acids long as established during the course of optimizing the length of the peptide and efficient positioning of the glycosylated epitope that is specifically recognized by auto-antibodies in patients. Throughout the specification, the length of 20 amino acids is used as a convenient length and to ensure that the entire epitope is encompassed within the peptide. While most epitopes will be on the order of 5-10 amino acid residues, and hence contained within a 20 amino acid peptide, any size peptide is possible if sufficient to contain the epitope for antibody detection. In turn, longer peptides may allow for incorporation of additional epitopes which could provide different selectivity for cancer.

#### Post-Translational Modification of Peptides

In some aspects, the invention relates to the identification of disease-associated PTM-peptides, wherein the PTM-peptide is selectively recognized by disease-associated antibodies. Preferably, the disease-associated antibodies recognize neither the peptide alone nor the PTM alone or attached to a different peptide. In other words, the antibody epitope comprises both part of the protein backbone and part of the PTM.

The PTM may be one or more modifications of one or more residues of the amino acid sequence. The PTM can be any of the known PTMs involving enzymatic modifications of amino acids including glycosylation, phosphorylation, citrinylation, acetylation, methylation (Anderton 2004; Doyle and Mamula 2005; Doyle and Mamula 2001).

All 20 primary amino acids used by man are capable of undergoing some type of PTM. However, certain factors determine whether those modifications will take place. First, the location of the amino acid within the protein sequence affects both the type and frequency of modifications that may arise. Flanking residues can influence the conformation of the protein, potentially altering whether an enzyme has access to

a certain amino acid or is exposed to a certain environment. The cellular location of the modifying enzyme, if required, will determine whether the modification occurs and disease-associated changes in localization of such enzymes may lead to aberrant posttranslational modifications. Previous modifications or proteolytic cleavages within a protein influence subsequent amino acid modifications within the same protein.

An exemplary PTM of the invention is mucin-type O-linked glycosylation (“O-glycosylation” or “O-linked glycosylation”). Examples of O-linked glycosylation include, e.g., the addition of N-acetyl-galactosamine (GalNAc), fucose, glucose, N-acetylglucosamine (GlcNAc), or mannose. GalNAc O-glycosylation is a particularly preferred PTM of the invention. GalNAc O-glycosylation is carried out by specific enzymes; for example, the addition of N-acetyl-galactosamine (GalNAc) to serine or threonine residues is carried out by the enzyme UDP-N-acetyl-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase (EC 2.4.1.41). Other types of O-glycosylation include  $\alpha$ Mannose,  $\alpha$ Fucose,  $\beta$ Glucose,  $\beta$ GlcNAc, and  $\beta$ Xylose glycosylation. Also contemplated by the present invention are other forms of glycosylation, such as, e.g., N-linked glycosylation, hydroxyl-lysine glycosylation, and C-mannosylation. Biosynthesis and structures of these types of protein glycosylation are reviewed in *Essentials of Glycobiology* (2<sup>nd</sup> edition, eds A. Varki, Cummings, Esko, Freeze, Stanley Bertozzi, Hart, Etzler. CSH Press 2009). It is to be understood that examples of PTM modification provided herein, such as O-glycosylation, are meant to be non-limiting examples which serve to prove the principal of the present methods (i.e., that the presently disclosed methods are useful for identifying PTM-modified peptides or peptide epitopes specifically recognized by disease-associated antibodies). The methods of the invention are also applicable, however, to proteins or peptides modified with other PTMs contemplated by the present invention, such as but not limited to phosphorylation, citrinylation, acetylation, and methylation.

In certain aspects of the invention, glycoproteins, glycopeptides and glycopeptide epitopes that are aberrantly glycosylated are provided. Examples of aberrant forms of O-glycans include, but are not limited to, truncated immature O-glycans such as Tn, T, and STn as well as non-sialylated and non-galactosylated core 2, 3 and 4 structures, shown in Table I below:

TABLE I

Representative mucin-type O-glycan structures on normal and diseased cells <sup>1</sup>				
Name	Hapten Structure (+/-Ser/Thr or artificial linker)	Type of Glycoconjugate	Distribution (main)	No
Tn	GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	1
STn	NeuAc $\alpha$ 2-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	2
T	Gal $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	3
mSTa	NeuAcA2-3Gal $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Normal cells	4
mSTb	NeuAcA2-3Gal $\beta$ 1-3[NeuAc $\alpha$ 2-6]GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Normal cells	5
Truncated C3	GlcNAc $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	6
Truncated C2	(NeuAc2-3) <sub>+</sub> /Gal $\beta$ 1-3[GlcNAc $\beta$ 1-6]GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	7
Truncated C4	GlcNAc $\beta$ 1-3[GlcNAc $\beta$ 1-6]GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	8
Non-capped type1-C3	Gal $\beta$ 1-3GlcNAc $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	9
Non-capped type2-C2	(NeuAc2-3) <sub>+</sub> /Gal $\beta$ 1-3[Gal $\beta$ 1-4GlcNAc $\beta$ 1-6]GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	10
Non-capped type2-C4	(Gal $\beta$ 1-4)GlcNAc $\beta$ 1-3[Gal $\beta$ 1-4GlcNAc $\beta$ 1-6]GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	11
GalNAca-Tn	GalNAc $\alpha$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	12



TABLE I-continued

Representative mucin-type O-glycan structures on normal and diseased cells <sup>1</sup>				
Name	Hapten Structure (+/-Ser/Thr or artificial linker)	Type of Glycoconjugate	Distribution (main)	No
SA-type1-C3	NeuAc $\alpha$ 2-3Gal $\beta$ 1-3GlcNAc $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	13
SLe <sup>a</sup> -C3	NeuAc $\alpha$ 2-3Gal $\beta$ 1-3[Fuc $\alpha$ 1-4]GlcNAc $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	Cancer cells	14
LacDiNAc-C3	GalNAc $\beta$ 1-3/4GlcNAc $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	unknown	15
LacDiNAc-C2	Gal $\beta$ 1-3[GalNAc $\beta$ 1-3/4GlcNAc $\beta$ 1-6]GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	unknown	16
LacDiNAc-C4	GalNAc $\beta$ 1-3/4GlcNAc $\beta$ 1-3[GalNAc $\beta$ 1-3/4GlcNAc $\beta$ 1-6]GalNAc $\alpha$ 1-O-Ser/Thr	O-linked	unknown	17

<sup>1</sup>Additional modifications such as capping terminal  $\beta$ 3/4Gal residues with Fuc $\alpha$ 1-2 (blood group H) and Gal(NAc) $\alpha$ 1-3 (blood group A,B) are generally produced by normal cells. Modifications such as 3/6-O-SO<sub>3</sub> of Gal and GalNAc, 9-O-acetylation of NeuAc, NeuGc instead of NeuAc, may also occur in normal and cancer cells.

In some aspects of the invention, the glycopeptide sequences of the invention may be derived from disease-associated proteins, such as, e.g., a glycoprotein specifically expressed on the cell surface of a cancer cell, but not on the surface of a non-malignant cell, or overexpressed on cancer cell surfaces, e.g., mucin 1 (MUC1) (GenBank Accession Nos. NP\_002447 (SEQ ID NO: 1); NP\_001018016 (SEQ ID NO: 2); NP\_001018017 (SEQ ID NO: 3); NP\_001037855 (SEQ ID NO: 54); NP\_001037856 (SEQ ID NO: 55); and NP\_001037857 (SEQ ID NO: 56)); MUC16 (GenBank Accession No. NP\_078966 (SEQ ID NO: 57); and mesothelin (MSLN) (GenBank Accession Nos. NP\_037536 (SEQ ID NO: 58) and NP\_005814 (SEQ ID NO: 59). In some embodiments, the glycoproteins are organ-specific glycoproteins. Examples of such glycoproteins include MUC16 (expressed in the female reproductive tract) and mesothelin, which is specifically expressed in the normal lung, but with cancer expression in ovarian and cervical cancers. Specific examples of other glycoproteins of the invention include, but are not limited to, human proteins predicted from the completed human genome containing one or more serine and/or threonine GalNAc O-glycosylation sites as predicted by the NetOGlyc algorithm.

Non-limiting examples of such proteins include cell membrane receptors such as low-density lipoprotein receptor precursor (LDLR) (GenBank Accession No. NP\_000518) (SEQ ID NO: 67)), very low-density lipoprotein receptor precursor (VLDLR) (GenBank Accession Nos. NP\_001018066 (SEQ ID NO: 68) and NP\_003374 (SEQ ID NO: 69)), and receptor tyrosine-protein kinase erbB-2 precursor (ERBB2) (GenBank Accession Nos. NP\_004439 (SEQ ID NO: 70) and NP\_001005862 (SEQ ID NO: 71)); chaperones such as heat shock 70 kDa protein 5 (HSPA5) (GenBank Accession No. NP\_005338 (SEQ ID NO: 72) and heat shock 70 kDa protein 8 (HSPA8) (GenBank Accession No. NP\_0694881) (SEQ ID NO: 73) and NP\_006588 (SEQ ID NO: 74); secreted cytokines, growth factors and glycoproteins such as interferon alpha-2 precursor (IFNA2) (GenBank Accession No. NP\_000596) (SEQ ID NO: 75), interleukin-2 (IL2) (GenBank Accession No. NP\_000577) (SEQ ID NO: 76), and inhibin beta B chain precursor (INHBB) (GenBank Accession No. NP\_002184) (SEQ ID NO: 77); proteases such as matrix metalloproteinase-14 precursor (MMP14) (GenBank Accession No. NP\_004986) (SEQ ID NO: 78); enzymes such as prostatic acid phosphatase precursor (ACPP) (GenBank Accession No. NP\_001127666) (SEQ ID NO: 79) and NP\_001090 (SEQ ID NO: 80); and mucins such as melanoma cell adhesion molecule (MCAM) (GenBank Accession No. NP\_006491) (SEQ ID NO: 81).

In other embodiments, glycopeptide mutants are contemplated for use in the present invention. For example, a peptide library can be generated wherein each amino acid in the peptide sequence around one or more sites for PTM modification (e.g., O-glycosylation) is varied by any combination of the 20 amino acids used in human proteins to form additional peptide sequences (i.e. mutants) with the same PTM motif.

In certain embodiments, the present invention further relates to the design of glycopeptide libraries for screening disease-associated antibodies and/or for identifying disease-associated glycopeptides and/or glycopeptide epitopes. In certain aspects, a glycopeptide library of the invention is provided as a glycopeptide panel for identifying glycopeptides reactive with disease-associated auto-antibodies. A "glycopeptide panel" comprises at least two glycopeptides (or indeed entire glycoproteins) and may be used in an antibody binding assay of the invention. In certain aspects, methods for designing both the sequence of the glycopeptide and the specific site(s) for glycosylation are provided.

Preferably, glycopeptides of the glycopeptide libraries of the invention are from about 4 to about 50 amino acids in length. More preferably, such glycopeptides are from about 4 to about 25 amino acid residues in length.

In certain aspects, peptides are designed as fragments of a glycoprotein. A random peptide library encompassing peptides having between about 4 and about 50 amino acids, is provided, wherein each amino acid in each peptide is varied by all 20 amino acids used in human proteins to form different peptide sequences. These random peptides are PTM-modified, e.g., O-glycosylated, on at least one amino acid residue. In other aspects, the peptide library comprises peptides covering all serine and threonine residues in the predicted human protein sequences. In yet another aspect, peptides of the glycopeptide libraries comprise sequences derived from disease-associated proteins and/or organ-specific proteins, as described, supra.

In certain embodiments of the invention, a peptide suitable for testing is a potential acceptor of GalNAc O-glycosylation by polypeptide GalNAc-transferases if: 1) the peptide is a sequence derived from the human proteome, wherein the human proteome may be predicted from the human genome; and 2) the peptide comprises one or more serine and/or threonine residues. Preferably, such peptides are derived from proteins that have a signal sequence. It is also preferred that such peptides have sequences that, in vitro, serve as substrates for one or more human polypeptide GalNAc-transferases, such as, e.g., GalNAc-T1, T2, T3, or T4. The initiating enzymes for other types of O-glycosylation that attaches the first sugar residue to Serine and Threonine residues of

polypeptides have been cloned and expressed recombinantly and hence these types of modifications are amiable to the same strategy for testing (Essentials of Glycobiology (2<sup>nd</sup> edition, eds A. Varki, Cummings, Esko, Freeze, Stanley Bertozzi, Hart, Etzler. CSH Press 2009).

In certain aspects, it is preferred that the glycopeptides of the invention comprise sequences predicted by the NetOGlyc algorithm. The NetOGlyc algorithm has been developed to predict sites and proteins modified by O-glycosylation and this has been postulated to have a positive prediction rate of 76% (Julenius et al. 2005).

In other embodiments, peptides may be modified with other PTM modifications.

#### Glycopeptide Synthesis

In some aspects of the invention, the peptide sequence of the glycopeptides of the invention can be synthesized using standard chemical synthesis [Meldal M, Bock K. A general approach to the synthesis of O- and N-linked glycopeptides. *Glycoconj J.* 1994; 11(2):59-63]. For example, GalNAc $\alpha$ -Ser/Thr-Fmoc, GlcNAc $\alpha$ -Ser/Thr-Fmoc, Man $\alpha$ -Ser/Thr, and Glc $\beta$ -Ser/Thr amino acids are commercially available (Sussex Inc (Canada)), and may be incorporated into the peptides during synthesis. The glycopeptides of the invention may be synthesized with and without an N-terminal linker for printing on epoxy or NHS-activated glass slides, respectively. In certain embodiments, glycopeptides may also be synthesized directly on microarray slides ("spot synthesis"). In other embodiments, peptides are previously synthesized and then immobilized or used in solution, according to a method of the present invention.

In certain aspects, the synthesized peptides or glycopeptides are O-glycosylated or further O-glycosylated using enzymatic synthesis of O-glycans at specific sites to form glycopeptides (Tarp and Clausen 2008).

In certain aspects of the present invention, the peptides may be glycosylated by a number of different methods, such as e.g., on-slide glycosylation, in solution glycosylation, or in vivo, e.g., by recombinant expression in appropriate host cells (Tarp et al. *Glycobiology* 2007).

Glycosylation may be achieved using one or more recombinant glycosyltransferases. such as, e.g., recombinant polypeptide GalNAc-transferases (e.g. GalNAc-T2, -T3 and -T4). See, e.g., U.S. Pat. No. 5,876,716 by Hansen and U.S. Pat. No. 6,465,220 by Hassan; see also, Bennett et al. 1998; Bennett et al. 1996; and White et al. 1995.

Further expansion may also be achieved using a recombinant sialyltransferase, ST6GalNAc-II, to produce STn glycoforms (structure no. 2, Table I) of the GalNAc glycopeptides. T glycoforms may be produced by a recombinant *Drosophila* core1  $\beta$ 3galactosyltransferase, truncated core3 glycoforms (structure no. 6, Table I) may be produced using a recombinant human  $\beta$ 3GlcNAc-transferase (Iwai et al. 2002), and non-capped type1-core3 glycoforms (structure no. 9, Table I) may be produced using  $\beta$ 3Gal-T5 (see, U.S. Pat. No. 7,332,279).

In other aspects, the glycopeptides and/or glycoproteins of the invention may be derived from recombinant or isolated glycopeptides or glycoproteins and further glycosylated or modified according to the methods of the present invention. For example, commercially available glycoprotein arrays (available, e.g., from Invitrogen), may be treated with exoglycosidases, e.g., neuraminidase,  $\beta$ galactosidase,  $\beta$ N-acetylglucosaminidase and other enzymes, in order to expose cancer-associated glycans, e.g., Tn or T, to form glycopeptides according to the present invention.

In certain aspects of the invention, the O-glycan is preferably positioned in the center of the peptide. While not intend-

ing to be bound by a specific theory, positioning the O-glycan in the center of the peptide may facilitate proper presentation of the O-glycan for specific antibody binding to a glycopeptide epitope. In certain aspects, for example, in a glycopeptide of 20 amino acid residues in length, the O-glycan is preferably attached to a serine or threonine amino acid residue placed at a site from about residue 6 to about residue 15 and more preferably from about residue 8 to about residue 13. For example, in the present Examples, glycopeptides were designed with a single GalNAc at position 12 (of the 20-mer) to allow optimal exposure of peptide sequence flanking the O-glycan, taking into consideration that the glycopeptides will be covalently linked primarily through the N-terminal amino acid.

In certain aspects, the O-glycans to be presented on a glycopeptide library of the invention may include all known O-glycan structures. In preferred embodiments, the glycopeptides comprise glycans known to be disease-associated, such as Tn, STn, T, Truncated C3, Truncated C2, Truncated C4, non-capped type1-C3, non-capped type2-C2, non-capped type2-C4, GalNAc $\alpha$ -Tn, SA-type1-C3, SLea-C3, LacDiNAc-C3, LacDiNAc-C2, and LacDiNAc-C4 (see Table I for additional non-limiting examples of such glycans). Further the O-glycans may be substituted with sulfation or other immunogenic substitutions including acetylation and artificial chemical groups.

#### Screening Assays

In certain embodiments, the present invention provides methods for identifying glycopeptides and/or glycopeptide epitopes reactive with disease-associated auto-antibodies using an assay comprising one or more glycopeptide panels. Preferably, such auto-antibodies bind glycopeptide epitopes through recognition of both the peptide portion and the glycan portion, but not through recognition of either the peptide or the glycan alone. The panel is contacted with a sample containing the disease-associated antibodies (e.g., sera obtained from an individual with the disease).

In a specific embodiment, the invention provides a method for identifying glycopeptides reactive with cancer-associated auto-antibodies, wherein the method comprises: (a) providing a panel comprising glycopeptides having a peptide portion and a glycan portion; (b) contacting the panel with an antibody-containing a sample from a patient with cancer; and (c) identifying glycopeptides in the panel that (i) are selectively recognized by antibodies in the sample, but not by antibodies in a control sample, and (ii) are recognized by such antibodies in the sample through recognition of both the peptide portion and the glycan portion, but not through recognition of either the peptide or the glycan alone.

Non-limiting examples of suitable antibody-containing samples for the assays of the present invention include serum, plasma, body fluids such as milk, saliva, mucosal secretions, feces, urine, cells and tissues, and any antibody preparations thereof.

Further, in order to develop the glycopeptide screening assays of the present invention, a control sample is used. By "control sample", it is meant a sample containing pooled sera obtained from apparently disease-free or healthy individuals (i.e., individuals who do not have the disease-associated antibodies in their serum because they do not have the relevant disease), or, it is meant multiple control samples, wherein each sample is obtained from a single apparently healthy (disease-free) individual, and then data obtained in the assay for the tested control samples are compared in order to exclude any samples from control individuals who are sus-

pected to in fact not be healthy, based on the presence of auto-antibodies not present in a statistically significant fraction of the control population.

In certain aspects, the present invention provides methods for identifying cancer-associated glycopeptide epitopes, wherein the epitope includes both part of the glycan of the glycopeptide and part of the peptide amino acid sequence. Such methods can comprise the following steps: (a) providing a panel comprising glycopeptides having a peptide portion and a glycan portion; wherein the peptide amino acid sequences of the glycopeptides are serially shifted 1-5 residues in either direction, to provide a series of overlapping peptide sequences; (b) contacting the panel with an antibody-containing sample from a patient with cancer; (c) identifying glycopeptides in the panel that (i) are selectively recognized by antibodies in the sample, but not by antibodies in a control sample, and (ii) are recognized by such antibodies in the sample through recognition of both the peptide portion and the glycan portion, but not through recognition of either the peptide or the glycan alone; and (d) mapping the minimal glycopeptide epitope based on the pattern of antibody binding to the overlapping glycopeptide sequences.

“Epitope mapping” may be carried out as follows: A glycopeptide epitope comprising e.g., a 20-mer glycopeptide with a single glycan attached to position 12 can be “mapped” in terms of peptide sequence requirement by synthesis of a panel of 20-mer glycopeptides in which each amino acid around the glycan site is modified one by one to an amino acid different from the one present in the identified glycopeptide, e.g. alanine or valine. Analysis of antibody binding to this panel of “walking” alanine or valine residues through the peptide sequence will demonstrate which residues abrogate binding, and thus provide information of the necessary peptide sequence backbone around the glycosylation site required for antibody binding.

In certain aspects of the invention, the minimum glycopeptide epitope is preferably about 2 to about 7 amino acid residues in length, but can extend to up to about 15 residues, and comprises a portion of an O-glycan modifying the glycopeptide epitope. In certain embodiments, the minimal glycopeptide epitope spans about 3 to about 4, about 2 to about 3, or about 1 to about 2 amino acid residues on each side of the O-glycan that is part of the minimal epitope identified by the methods of the present invention. In other embodiments, a greater number of amino acids may be present on one side of the O-glycan compared to the number of amino acids of the minimal epitope on the other side of the O-glycan. The minimum glycopeptide epitope can be, for example, a “minimum cancer-associated glycopeptide epitope,” which is the minimum glycopeptide epitope identified by the methods of the present invention to be specifically recognized by a cancer-associated auto-antibody.

In certain embodiments, the epitope structure of the glycopeptide epitopes identified by the present methods is determined by mass spectrometry.

In some aspects, determining whether glycopeptides and/or glycopeptide epitopes are selectively recognized by antibodies in a sample through recognition of both the peptide portion and the glycan portion, wherein the antibodies do not recognize either portion alone, may be achieved as follows: an additional panel may be provided, in which the unglycosylated forms of the glycopeptides are provided (i.e., the corresponding peptides) and antibody binding is determined. In order for a glycopeptide to be selectively recognized by an antibody in the sample, antibody binding to the corresponding peptide should be partially or preferably completely abrogated. Preferably, antibody binding to the corresponding pep-

ptide is diminished by at least about 40%, preferably at least about 50%, more preferably at least about 60%, even more preferably at least about 70%, still more preferably at least about 80%, more preferably at least about 85%, still more preferably at least about 90%, and most preferably 95% to 100% compared to antibody binding to the glycopeptide.

In other aspects of the present invention, methods of determining the presence of auto-antibodies binding O-glycopeptides, may also comprise the step of contacting the panel with a peptide inhibitor in order to exclude antibodies that recognize the non-glycosylated form of the glycopeptide. Peptide inhibitors are typically a peptide of the same amino acid sequence as the glycopeptide, however, without any glycosylations.

In other embodiments, antibodies that recognize only the hapten glycan or the glycan-conjugated to a different peptide or artificial carrier may be excluded, in order to prevent identification of epitopes that consist only of the glycan hapten. This can be achieved in several ways. For example, in certain embodiments, hapten-specific antibodies may be removed from the sample prior to analysis.

In some embodiments, hapten-specific antibodies may be removed by affinity chromatography with an appropriate resin with covalently linked carbohydrate haptens, or by inhibition with carbohydrate haptens in solution during binding assays. An example of preferable resin is GalNAc-Sepharose or other appropriate resins that would be able to bind anti-Tn hapten antibodies. Other preferable resins are GlcNAc-Sepharose, Man-Sepharose, Glc-Sepharose or Fuc-Sepharose and without limitations corresponding di- and trisaccharides in the biosynthetic pathways bound resins.

In other embodiments, hapten-specific antibodies may be excluded from binding to glycopeptides in the binding assays of the present invention using a carbohydrate inhibitor. In some embodiments, the carbohydrate inhibitor comprises a normal occurring O-glycan such as sialylated or fucosylated core 2, 3, or 4 O-glycan, as is typically present in normal cells. In some aspects, the carbohydrate inhibitor may be Tn, STn, T or other truncated O-glycan structures based on core 3 or 4. Also preferred are polyvalent PAA (polyacrylamide) conjugates (GlycoTech, US) of the aforementioned carbohydrates. Still in another embodiment, the carbohydrate inhibitor is a monosaccharide such as GalNAc, GlcNAc, Gal, Glc, Fuc, Man, Xyl and NeuAc. It will be apparent to the skilled artisan that other combinations of carbohydrates will have the same effect.

The above-described methods, as well as other methods that may be readily determined by a skilled artisan and used to achieve the same effect, may be used to exclude antibodies in a sample that do not specifically recognize the glycopeptide (i.e., through both the peptide and the glycan). In certain embodiments of the invention, exclusion of such antibodies from the analysis is necessary in order to identify the glycopeptides and glycopeptide epitopes that are specifically recognized by disease-associated antibodies.

In certain embodiments, a peptide inhibitor and/or an O-glycan inhibitor may be immobilized on a solid support, which is used to remove antibodies that interact with the peptide inhibitor and/or with the O-glycan carbohydrate inhibitor from a sample, prior to use of the sample according to a method of the present invention.

In some aspects, the screening assays of the present invention involve immobilized glycopeptides; however, in solution assays such as polarization, inhibition and competitive binding assays are also contemplated for use in the present invention. [See, e.g., Smith D S, Eremin S A. Fluorescence polarization immunoassays and related methods for simple, high-

throughput screening of small molecules. Anal Bioanal Chem. 2008; 391(5):1499-507.]

Non-limiting examples of screening assays involving immobilized glycopeptides contemplated for use in the present invention include antibody-binding assays, such as enzyme-linked immunosorbent assay (ELISA), multiplex bead arrays (see, Elshal et al., (2006) Methods; 38(4):317-323); BiaCore SPR analysis where binding affinities can be evaluated and microarray platforms.

In a preferred embodiment, glycopeptide libraries of the invention are immobilized on microarray slides. The glycopeptides may be printed on microarray slides, such as, e.g., Corning, Scineion or Nexterion® Slide H or Schott Nexterion® Slide H MPX 16 (Schott AG, Mainz, Germany) by JPT (Germany). Printing may be carried out using MicroGrid, ArrayIT or similar according to the methods described in (Blixt O, Head S, Mondala T, Scanlan C, Huflejt ME, Alvarez R, Bryan MC, Fazio F, Calarese D, Stevens J, Razi N, Stevens DJ, Skehel JJ, van Die I, Burton DR, Wilson IA, Cummings R, Bovin N, Wong CH, Paulson JC. Printed covalent glycan array for ligand profiling of diverse glycan binding proteins. Proc Natl Acad Sci USA. 2004; 101(49):17033-8)

Microarray slides of the invention may also be prepared by companies such as Schott (Louisville, Ky.), ArrayIt Corp. (Sunnyvale, Calif.), or Scineon (Germany).

In certain embodiments, assays for large scale screening include, e.g., multiplex bead or array formats where many targets can be assayed simultaneously with very little consumption of antibody. For example, a small volume (50 µl) of an antibody-containing sample (e.g. serum or diluted serum) may be incubated with a solution of beads, wherein each bead is coated with a specific glycopeptide, and each bead possesses a distinguishing characteristic (e.g., size) that allows it to be differentiated from other beads in the sample. If an antibody is present in the sample that recognizes a glycopeptide on one of the beads, it will bind to the bead. Then, specific binding of antibodies to each glycopeptide in the sample may be detected using a detecting reagent, such as, e.g., biotinylated anti-Ig antibody followed by fluorescently-labeled streptavidin. The concentration of antibody in the sample that is specific for each glycopeptide on the bead may then be quantified using a bead analyzer, such as, e.g., the Luminex® 200™ System (Invitrogen).

In yet another embodiment of the invention, the detection of auto-antibodies can be limited to distinct human Ig isotypes and subclasses. Most human natural carbohydrate antibodies are of IgM isotype and it is the detection of auto-antibodies of IgG isotype and subclasses is preferred. More specifically, detection of binding of human IgG antibodies, or IgG1, 2, 3, and 4 individually, with appropriate anti-human antibodies avoid most reactivity with truncated O-glycan haptens such as Tn, STn, T core3, and other truncated structures to which IgM antibodies are found in control samples. Methods of Diagnosing

In some aspects, the present invention provides methods for diagnosing a patient with a disease. For example, disease-associated glycopeptides and glycopeptide epitopes identified by the methods of the present invention may be used for detection of disease-associated auto-antibodies with the purpose of determining diagnosis and/or prognosis.

For example, in certain embodiments, a patient may be diagnosed as having cancer or as not having cancer, based on the presence or absence, respectively, of specific, cancer-associated glycopeptide-reactive auto-antibodies. In a specific embodiment, the method comprises contacting an antibody-containing sample from a patient with a panel comprising peptides, wherein at least a plurality of the pep-

ptides are glycopeptides. Further, each glycopeptide comprises a glycopeptide epitope that has been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera. It is then determined if antibodies in the sample are bound to glycopeptides of said panel; and concluded either that the patient has cancer if the sample comprises antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have cancer if the sample does not comprise antibodies that bind to at least one glycopeptide in the panel.

In certain aspects, the specific type of cancer that may be diagnosed or treated by a method of the present invention without limitation may be selected from the group consisting of breast cancer, colon cancer, ovarian cancer, cervical cancer, pancreatic cancer, prostatic cancer, liver cancer, kidney cancer, brain cancer, hematological cancers, testis cancer, head and neck cancers, and lung cancer.

In yet another embodiment, the diagnostic panel comprises glycopeptides comprising one or more and preferably at least 8 of the amino acid sequences selected from the group consisting of SEQ ID NOs. 15, 36, 49, and 82-146.

In yet another specific embodiment, the diagnostic panel comprises glycopeptides comprising one or more of the amino acid sequences selected from the group consisting of SHHSDSEDELVTDFPTDLPA (SEQ ID NO: 15); TPTP-KEKPEAGTYSVNNGND (SEQ ID NO: 36); SESFPHPG-FNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPT-KDIFTGLI (SEQ ID NO: 86); TDCGGPKDHPLTCDDPRFQA (SEQ ID NO: 109); PGT-STTPSQPNSAGVQDTEM (SEQ ID NO: 116); TKT-DASSTHHSTVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTR-PALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQAT-DTFSTVPPTPPSI (SEQ ID NO: 146). Furthermore, these glycopeptides may be O-glycosylated at one or more sites according to the methods of the present invention.

In yet another embodiment, the diagnostic panel comprises at least 8 glycopeptides, for example between about 8 and about 30 glycopeptides, such as 10, 12, 15, or 20 glycopeptides. A number of glycopeptides in excess of 30 is also within the invention. The upper limit of glycopeptides in a panel is limited by practical considerations (e.g., how many glycopeptides can fit on a substrate) or cost-benefit considerations. Preferably the glycopeptides are selected from the group consisting of SEQ ID NOs 15, 36, 49, and 82-146.

In yet other aspects, a patient may be diagnosed as having an autoimmune disease. In certain embodiments, the autoimmune disease is selected from the group consisting of coeliac disease, type I diabetes, multiple sclerosis, thyroiditis, Grave's disease, systemic lupus erythematosus, scleroderma, psoriasis, rheumatoid arthritis, alopecia areata, ankylosing spondylitis, Churg-Strauss Syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behcet's disease, Crohn's disease, dermatomyositis, glomerulonephritis, Guillain-Barre syndrome, inflammatory bowel disease (IBD), lupus nephritis, myasthenia gravis, myocarditis, pemphigus/pemphigoid, pernicious anemia, polyarteritis nodosa, polymyositis, primary biliary cirrhosis, rheumatic fever, sarcoidosis, Sjogren's syndrome, ulcerative colitis, uveitis, vitiligo, and Wegener's granulomatosis.

Thus, in some embodiments, a diagnostic panel of the invention comprises glycopeptide epitopes determined by the

methods of the present invention to be associated with an autoimmune disease. For example, in certain embodiments, a patient may be diagnosed as having an autoimmune disease or as not having an autoimmune disease, based on the presence or absence, respectively, of specific, autoimmune disease-associated glycopeptide-reactive auto-antibodies. In a specific embodiment, the method comprises contacting an antibody-containing sample from a patient with a panel comprising peptides, wherein at least a plurality of the peptides are glycopeptides. Further, each glycopeptide comprises a glycopeptide epitope that has been previously determined (i) to be selectively recognized by a subset of antibodies in sera from patients with a specific autoimmune disease, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera. It is then determined if antibodies in the sample are bound to glycopeptides of said panel; and concluded either that the patient has the autoimmune disease if the sample comprises antibodies that bind to at least one of the glycopeptides in the panel; or that the patient does not have the autoimmune disease if the sample does not comprise antibodies that bind to at least one glycopeptide in the panel.

#### Preparation of Antibodies

Other aspects of the present invention are antibodies prepared using one or more glycopeptides identified using the methods of the present invention, methods for preparation of these antibodies, and the use of such antibodies in therapy and diagnosis.

Yet another aspect of the present invention is a method for the preparation of hybridoma cells, which secrete monoclonal antibodies specific for the glycopeptides of the invention. One such method involves immunizing a suitable mammal with a glycopeptide of the invention; fusing antibody-producing cells of the mammal with cells of a continuous cell line; the hybrid cells obtained in the fusion are cloned; and cell clones secreting the desired antibodies are selected.

Still another aspect is a monoclonal antibody selected from the group consisting of: a monoclonal antibody produced by the hybridoma cells prepared by the method described above; and a monoclonal antibody prepared by molecular display techniques, such as mRNA display, ribosome display, phage display and covalent display against a glycopeptide of the invention.

For preparation of monoclonal antibodies, any technique that provides for the production of antibody molecules by continuous cell lines in culture may be used. These include but are not limited to the hybridoma technique originally developed by Kohler and Milstein (*Nature*, 1975; 256:495-497), as well as the trioma technique, the human B-cell hybridoma technique (Kozbor et al., *Immunology Today*, 1983; 4:72, Cote et al., *Proc. Natl. Acad. Sci. U.S.A.*, 1983; 80:2026-2030), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96, 1985). In an additional embodiment of the invention, monoclonal antibodies can be produced in germ-free animals (International Patent Publication No. WO 89/12690, published 28 Dec., 1989).

According to the invention, techniques described for the production of single chain antibodies (U.S. Pat. Nos. 5,476,786 and 5,132,405 to Huston; U.S. Pat. No. 4,946,778) can be adapted to produce glycopeptide-specific single chain antibodies. Indeed, these genes can be delivered for expression in vivo to, e.g., express a glycopeptide-specific antibody. An additional embodiment of the invention utilizes the tech-

niques described for the construction of Fab expression libraries (Huse et al., *Science*, 1989; 246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity for a glycopeptide or glycopeptide epitope of the invention.

Antibody fragments which contain the idiotype of the antibody molecule can be generated by known techniques. For example, such fragments include but are not limited to: the F(ab')<sub>2</sub> fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragments which can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragment, and the Fab fragments which can be generated by treating the antibody molecule with papain and a reducing agent.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, e.g., radioimmunoassay, ELISA (enzyme-linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitin reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), Western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In other embodiments, alternative techniques such as mRNA display, ribosome display, phage display and covalent display may also be used. These are all display techniques where a peptide library is selected against the glycopeptide. Such techniques can e.g. be used to identify humanized or fully human antibodies.

In a preferred embodiment, the monoclonal antibody binds an O-glycoprotein containing the O-glycopeptide epitope on cancer cells but not on a non-malignant counterpart.

In another preferred embodiment, the monoclonal antibody binds preferentially to the O-glycoprotein that is aberrantly glycosylated and expressed on cancer cells.

In still another embodiment, the monoclonal antibody binds to or at least interacts directly with the O-glycopeptide.

In a preferred embodiment, the antibody prepared using a glycopeptide of the invention is humanized or fully human, such as to decrease the immunogenicity of the antibody in humans. This is typically desirable if the antibody is used as a therapeutic. However, in some situations a rapid clearance may be desired, wherefore non-humanized antibodies are also of interest as therapeutics. One such situation can, e.g., be when administering antibody conjugates where antibodies are coupled to toxins or radioisotopes. Such conjugated antibodies should either find their target rapidly or be cleared as they have a general toxic effect. Thus, one embodiment of the invention is conjugated antibodies. Non-limiting examples of antibody conjugates include radioisotopes, such as <sup>131</sup>I, <sup>90</sup>Y, <sup>177</sup>Lu (Leutitium (<sup>177</sup>Lu)) and <sup>67</sup>Cu (Copper (<sup>67</sup>Cu)); toxins, such as the fungal toxin maytansanoid (DM-1); and antibiotics, such as e.g., calicheamicin [See, Ross et al. *Antibody-based therapeutics: Focus on prostate cancer. Cancer and Metastasis Reviews* 24: 521-537, 2005].

#### Compositions and Uses

In certain embodiments, the present invention provides compositions comprising one or more disease-associated

glycopeptides and/or glycopeptide epitopes identified by the methods of the present invention. In certain aspects, such disease-associated glycopeptides comprise epitopes specifically recognized and bound by disease-associated antibodies.

In a specific embodiment, a composition of the invention comprises one or more of a glycoprotein or glycopeptide comprising an amino acid sequence selected from the group consisting of SEQ IDs 15, 36, 49, and 82-146. Preferably, the composition comprises one or more of a glycoprotein or glycopeptides comprising an amino acid sequence selected from the group consisting of SHHSDEDELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEKPEAGTYSVNNNGND (SEQ ID NO: 36); SESFPHPGFNMSLLENHTRQ (SEQ ID NO: 49); LAKMYYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGG-PKDHLPTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQP-NSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHH-STVPPLTSSN (SEQ ID NO: 132); HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134); ASRYNLTISDVSVDVPPFP (SEQ ID NO: 135); VPVTR-PALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQAT-DTFSTVPPTPSI (SEQ ID NO: 146). In certain embodiments, such glycoproteins or glycopeptides are further modified at at least one amino acid residue, with an O-glycan. Preferably, the amino acid residue is serine or threonine residue.

In some aspects, the invention provides methods for eliciting an immune response in an individual, wherein the immune responses is specific for one or more glycopeptides or glycoproteins identified by the methods of the present invention.

One aspect of the invention is a method of treating cancer or an autoimmune disease comprising administering a pharmaceutical composition of the invention. In a specific embodiment, a cancer patient is treated by eliciting an anti-cancer immune response that attacks cancer cells (e.g., tumors). In any of the aspects of the invention, the immune response elicited by a pharmaceutical composition of the invention may be an adaptive T and/or B cell response (e.g., either a cytotoxic T cell response or an antibody response, or both) directed against the cancer cells, which results in reduction or elimination of the cancer cells.

“Treating” or “treatment” of a state, disorder or condition includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human or other mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to an individual to be treated is either statistically significant or at least perceptible to the patient or to the physician.

#### Pharmaceutical Compositions and Administration

While it is possible to use a composition provided by the present invention for therapy as is, it may be preferable to administer it in a pharmaceutical formulation, e.g., in admixture with a suitable pharmaceutical excipient, diluent, or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Accordingly, in one aspect, the present invention provides a pharmaceutical composition or formulation comprising at least one composition of the invention, or a pharmaceutically acceptable

derivative thereof, in association with a pharmaceutically acceptable excipient, diluent, and/or carrier. The excipient, diluent and/or carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention can be formulated for administration in any convenient way for use in human or veterinary medicine.

#### Pharmaceutical Carrier

The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Alternatively, the carrier can be a solid dosage form carrier, including but not limited to one or more of a binder (for compressed pills), a glidant, an encapsulating agent, a flavorant, and a colorant. Suitable pharmaceutical carriers are described in “Remington’s Pharmaceutical Sciences” by E. W. Martin (1990, Mack Publishing Co., Easton, Pa. 18042).

#### Vaccines

In certain aspects, a disease-associated glycopeptide or glycoprotein of the present invention is provided in a vaccine. Thus, in certain aspects, such a disease-associated glycopeptide or glycoprotein is provided as an “immunogen” for inducing an immune response. In some aspects, a vaccine of the present invention is useful for treating cancer by inducing an “anti-cancer immune response.” Preferably, a vaccine of the present invention is effective for inducing an adaptive immune response that selectively target cancer cells and has minimal reactivity with normal cells.

In certain embodiments, the glycopeptide epitopes identified by the methods of the present invention are targets for spontaneously-induced human auto-antibodies. Thus, it is evident that these epitopes are not generally covered by immunological tolerance. Accordingly, in certain aspects of the invention, a vaccine comprising a glycopeptide immunogen identified by the present methods does not require an adjuvant.

In other embodiments, a vaccine comprising a glycopeptide immunogen of the invention may additionally contain adjuvants to induce or enhance the desired immune response, such as, e.g., an anti-cancer immune response. Exemplary adjuvants include, but are not limited to, cholera toxin, fragments and mutants or derivatives with adjuvant properties, *E. coli* heat-labile enterotoxin, fragments and mutants or derivatives with adjuvant properties, oil-in-water and water-in-oil emulsions, toll-like receptor ligands such as muramyl dipeptide, *E. coli* LPS, oligonucleotides comprised of unmethylated DNA, poly I:C, lipoteichoic acid, peptidoglycan. Enterotoxins and their adjuvant active derivatives such as cholera toxin, heat-labile *E. coli* enterotoxin, pertussis toxin, shiga toxin and analogs. Other adjuvants can be used such as complete Freund’s adjuvant, incomplete Freund’s adjuvant, saponin, mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil or hydrocarbon emulsions, keyhole limpet hemocyanins, and potentially useful human adjuvants such as N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl-D-isoglutamine, N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine, BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. An adjuvant can serve as a tissue depot that

slowly releases the antigen and also as a lymphoid system activator that non-specifically enhances the immune response (Hood et al., Immunology, Second Ed., 1984, Benjamin/Cummings: Menlo Park, Calif., p. 384). Where the vaccine is intended for use in human subjects, the adjuvant should be pharmaceutically acceptable.

#### Formulations

The compositions, vaccines and formulations of the present invention may comprise pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435 1712 which are herein incorporated by reference.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants, preserving, wetting, emulsifying, and dispersing agents. The pharmaceutical compositions may be sterilized by, for example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured using sterile water, or some other sterile injectable medium, immediately before use.

#### Administration and Dosage

The compositions (e.g., pharmaceutical or vaccine compositions) and formulations of the present invention can be administered topically, parenterally, orally, by inhalation, as a suppository, or by other methods known in the art. The term "parenteral" includes injection (for example, intravenous, intraperitoneal, epidural, intrathecal, intramuscular, intraluminal, intratracheal or subcutaneous). The preferred routes of administration are subcutaneous and intravenous.

The compositions and formulations of the present invention may be administered to an animal, preferably a mammal, and most preferably a human.

The dosage of the compositions or formulations of the present invention will vary widely, depending upon the nature of the disease, the patient's medical history, age, body weight, sex, sensitivity, the frequency of administration, the manner and route of administration, the clearance of the agent from the host, dosage period, drugs used in combination, and the like. The initial dose may be larger, followed by smaller maintenance doses.

For any composition or formulation used in the methods of the invention, the therapeutically effective dose can be estimated initially from animal models. Dose-response curves derived from animal systems are then used to determine testing doses for the initial clinical studies in humans. In safety determinations for each composition, the dose and frequency of administration should meet or exceed those anticipated for use in the clinical studies.

Toxicity and therapeutic efficacy of the compositions, vaccines, and formulations of the invention can be determined by

standard pharmaceutical procedures in experimental animals, e.g., by determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it can be expressed as the ratio ED<sub>50</sub>/LD<sub>50</sub>. Compositions that exhibit large therapeutic indices are preferred.

The data obtained from the animal studies can be used in formulating a range of doses for use in humans. The therapeutically effective doses of in humans lay preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. Ideally, a single dose of each drug should be used daily.

The compositions of the invention will typically contain an effective amount of the compositions for achieving the desired effect. As used herein, an "effective amount of a glycopeptide" is an amount that elicits the desired response upon administration, e.g., an amount that elicits an immune response in a mammal.

Administration of the compositions or formulations of the invention may be once a day, twice a day, or more often, but frequency may be decreased during a maintenance phase of the disease or disorder, e.g., once every second or third day instead of every day or twice a day. The dose and the administration frequency will depend on the clinical signs, which confirm maintenance of the remission phase, with the reduction or absence of at least one or more preferably more than one clinical signs of the acute phase known to the person skilled in the art. More generally, dose and frequency will depend in part on recession of pathological signs and clinical and subclinical symptoms of a disease condition or disorder contemplated for treatment with the present compounds.

The appropriate dose and dosage times under certain conditions can be determined by the test based on the above-described indices but may be refined and ultimately decided according to the judgment of the practitioner and each patient's circumstances (age, general condition, severity of symptoms, sex, etc.) according to standard clinical techniques.

In certain embodiments of the invention, use of an appropriate vaccine design and immunization scheme will therefore elicit immunity to a glycopeptide epitope of the immunogen and efficiency of the immunization can be monitored by immunoassays, e.g., by detecting the presence of immunogen-specific antibodies in an antibody-containing sample from an immunized patient by ELISA or other assay suitable for detecting antigen-specific antibodies.

Keeping the above description in mind, typical dosages of the glycopeptide-containing compositions of the invention are 5-50 µg glycopeptides conjugated to e.g. KLH (keyhole-Limpet Hemocyanin) given subcutaneously 3-5 times with 2-3 weeks apart. Maintenance vaccine could be extended with monthly or bi-monthly dosing for extended periods.

#### Kits

In some embodiments, the invention relates to a kit comprising one or more glycopeptides identified by the present methods. In certain aspects the kit comprises a panel of two or more glycopeptides identified by the present methods. In other aspects, the kit further provides instructions for use. In a specific embodiment, the kit provides a diagnostic assay for diagnosing cancer, comprising a panel of cancer-associated glycopeptides, assay buffers, and instructions for use.

In accordance with the present invention, there may be employed conventional molecular biology, microbiology, recombinant DNA, immunology, cell biology and other

related techniques within the skill of the art. See, e.g., Sambrook et al., (2001) Molecular Cloning: A Laboratory Manual. 3rd ed. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, N.Y.; Sambrook et al., (1989) Molecular Cloning: A Laboratory Manual. 2nd ed. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, N.Y.; Ausubel et al., eds. (2005) Current Protocols in Molecular Biology. John Wiley and Sons, Inc.: Hoboken, N.J.; Bonifacino et al., eds. (2005) Current Protocols in Cell Biology. John Wiley and Sons, Inc.: Hoboken, N.J.; Coligan et al., eds. (2005) Current Protocols in Immunology, John Wiley and Sons, Inc.: Hoboken, N.J.; Coico et al., eds. (2005) Current Protocols in Microbiology, John Wiley and Sons, Inc.: Hoboken, N.J.; Coligan et al., eds. (2005) Current Protocols in Protein Science, John Wiley and Sons, Inc.: Hoboken, N.J.; Enna et al., eds. (2005) Current Protocols in Pharmacology John Wiley and Sons, Inc.: Hoboken, N.J.; Hames et al., eds. (1999) Protein Expression: A Practical Approach. Oxford University Press: Oxford; Freshney (2000) Culture of Animal Cells: A Manual of Basic Technique. 4th ed. Wiley-Liss; among others. The Current Protocols listed above are updated several times every year.

EXAMPLES

The present invention is described further below in working examples which are intended to further describe the invention without limiting the scope therein.

Example 1

Development of a Cancer-Associated O-Glycopeptide Library for Microarray Display

GalNAc-Ser/Thr-Fmoc amino acids were synthesized by Sussex Inc (Canada) and 20-mer peptides and corresponding glycopeptides with one GalNAc O-glycan synthesized and printed on epoxy activated glass slides by JPT Peptide Technologies (Berlin, Germany). A total of 48 paired peptides and 48 GalNAc-glycopeptides were synthesized and printed (Table II).

TABLE II

Synthetic 96 paired glycopeptide 20-mer library derived from confirmed O-glycoproteins*		
SEQ ID NO:	Peptide No.	
4	1	TSAPDTRPAPGSTAPPAHGV
4	2	TSAPDTRPAPG <u>ST</u> APPAHGV
5	3	SAPDTRPAPGSTAPPAHGV
5	4	SAPDTRPAPG <u>ST</u> APPAHGV
6	5	PGSTAPPAHGVTSAPDTRPA
6	6	PGSTAPPAHGV <u>TS</u> APDTRPA
7	7	GSTAPPAHGVTSAPDTRPAP
7	8	GSTAPPAHGV <u>TS</u> APDTRPAP
8	9	PPAHGVTSAPDTRPAPGSTA
8	10	PPAHGVTSAPD <u>TR</u> PAPGSTA
9	11	FYLAMPFATPMEAEARRSL
10	12	KFSEFWDLDPEVRPTSAAVA
11	13	PLVEQGRVRAATVGSLAGQP
11	14	PLVEQGRVRAA <u>T</u> VGSLAGQP
12	15	LWSLCWSLAIAATPLPPTSAH
12	16	LWSLCWSLAIA <u>T</u> PLPPTSAH
13	17	LEACVIQGVGVTEPLMKED
13	18	LEACVIQGVGV <u>T</u> EPLMKED
14	19	KKWVQDSMKYLQKSPTPKP
15	20	SHHSDESDELVTDFPTDLPA
15	21	SHHSDESDELV <u>T</u> DFPTDLPA
16	22	DESDELVTDFPTDLPA <u>T</u> EVF
16	23	DESDELVTDFP <u>T</u> DLPA <u>T</u> EVF
17	24	FPTDFPTDLPA <u>T</u> EVFTPVVP

TABLE II-continued

Synthetic 96 paired glycopeptide 20-mer library derived from confirmed O-glycoproteins*		
SEQ ID NO:	Peptide No.	
17	25	FPTDFPTDLPA <u>T</u> EVFTPVVP
18	26	FPTDLPA <u>T</u> EVFTPVVPTVDT
18	27	FPTDLPA <u>T</u> EVFTPVVPTVDT
19	28	PATEVFTPVVPTVDTYDGRG
19	29	PATEVFTPVVPT <u>V</u> DTYDGRG
20	30	PGAQGLPGVGLTPSAAQTAR
20	31	PGAQGLPGVGL <u>T</u> PSAAQTAR
21	32	RGETRCEQDRPSPTTAPPAP
21	33	RGETRCEQDRP <u>S</u> PTTAPPAP
22	34	ETRCEQDRPSPTTAPPAPPS
22	35	ETRCEQDRPSPT <u>T</u> APPAPPS
23	36	TRCEQDRPSPTTAPPAPPS
23	37	TRCEQDRPSPT <u>T</u> APPAPPS
24	38	PSPTTAPPAPSPSPVVPK
24	39	PSPTTAPPAPSPSPVVPK
25	40	PTTAPPAPSPSPVVPKSP
25	41	PTTAPPAPSPSPVVPKSP
26	42	TAPPAPSPSPVVPKSPSV
26	43	TAPPAPSPSPVVPKSPSV
27	44	STNEFLCDKDKTSTVAPTHI
27	45	STNEFLCDKDK <u>T</u> STVAPTHI
28	46	NEFLCDKDKTSTVAPTHIHT
28	47	NEFLCDKDKT <u>S</u> TVAPTHIHT
29	48	CDKDKTSTVAPTHIHTVPS
29	49	CDKDKTSTVAP <u>T</u> IHTVPS
30	50	DKTSTVAPTHIHTVPSPTT
30	51	DKTSTVAPTHI <u>T</u> VPSPTT
31	52	KTSTVAPTHIHTVPSPTT
31	53	KTSTVAPTHIHT <u>T</u> VPSPTT
32	54	TVAPTHIHTVPSPTTTPK
32	55	TVAPTHIHTVPS <u>P</u> TTTPK
33	56	APTHIHTVPSPTTTPK
33	57	APTHIHTVPSPT <u>T</u> TPK
34	58	PTIHTVPSPTTTPK
34	59	PTIHTVPSPT <u>T</u> TPK
35	60	TIHTVPSPTTTPK
35	61	TIHTVPSPTT <u>T</u> PK
36	62	TPTPKPEAGTYSVNNNGND
36	63	TPTPKPEAG <u>T</u> YSVNNNGND
37	64	ACLAVSAGPVPTPPDNIQVQ
37	65	ACLAVSAGPV <u>P</u> TPPDNIQVQ
38	66	RRAVLPQEEEGSGGGQLVTE
38	67	RRAVLPQEEEG <u>S</u> GGGQLVTE
39	68	LNAVNSLTPQSTKVPSLFE
39	69	LNAVNSLTPQ <u>S</u> TKVPSLFE
40	70	NAVNSLTPQSTKVPSLFE
40	71	NAVNSLTPQ <u>S</u> TKVPSLFE
41	72	TFVLSALQSPSTHSSNTQR
41	73	TFVLSALQSP <u>S</u> THSSNTQR
42	74	RQGWALRPVLPQSAHDPPA
42	75	RQGWALRPVLP <u>Q</u> SAHDPPA
43	76	QKKAKNLDAITTPDPTTAS
43	77	QKKAKNLDAIT <u>T</u> PDPTTAS
44	78	FLSLSQGQESQTELPNPRIS
44	79	FLSLSQGQESQ <u>T</u> ELPNPRIS
45	80	LSLALVTNSAPTSSSTKKTQ
45	81	LSLALVTNSAP <u>T</u> SSSTKKTQ
46	82	LISPLAQAVRSSSRTPSDKP
46	83	LISPLAQAVRSSSR <u>T</u> PSDKP
47	84	DDENTAQFVHVSESFHPGF
47	85	DDENTAQFVHV <u>S</u> ESFHPGF
48	86	SESFHPGFNMSLLENHTRQ
48	87	SESFHPGFNMS <u>L</u> LENHTRQ
49	88	SGWGSIEPENFSFPDDLQCV
49	89	SGWGSIEPEN <u>F</u> SFPDDLQCV
50	90	RIQRGPGRAFVTIGKIGNMR
50	91	RIQRGPGRAFV <u>T</u> IGKIGNMR
51	92	EMSRHSLEQKPTDAPPKVLT
51	93	EMSRHSLEQK <u>P</u> TDAPPKVLT
52	94	CSESLELEDPSGLGVTKQD
52	95	CSESLELEDPS <u>G</u> LVTKQD
53	96	LLEFYLAMPFATPMEAEAR

\*Indicates attachment site of GalNAc residues to Ser/Thr (bold, underlined).



Glycopeptides were synthesized with and without N-terminal linker for printing on epoxy or NHS-activated glass slides, respectively. Peptides were designed based on known O-glycoproteins using the algorithm NetOGlyc for selection of O-glycosylation sites (Julenius et al. 2005), which in most cases coincides with experimentally determined O-glycosylation found on isolated proteins, as these glycoproteins have served as a training set for the algorithm. Glycopeptides were designed with a single GalNAc at position 12 to allow optimal exposure of peptide sequence flanking the O-glycan taking into consideration that the glycopeptides will be covalently linked primarily through the N-terminal amino acid. Glycopeptides were synthesized at 100 nmol scale using step-wise blocking by acetylation and printing directly with theoretical excess of 50 fold onto slides.

In one group, the paired peptide and single GalNAc glycopeptide library was further expanded by on-slide glycosylation with one or more recombinant glycosyltransferases to enhance the number of GalNAc O-glycosylation sites using one or more recombinant polypeptide GalNAc-transferases (e.g., GalNAc-T2, -T3 and -T4) (see, U.S. Pat. Nos. 5,876,716 and 6,465,220) (Bennett et al. 1998; Bennett et al. 1996; White et al. 1995)(see also, FIG. 1). Further expansion was achieved by use of a recombinant sialyltransferase, ST6GalNAc-II, to produce STn glycoforms (structure no. 2, Table I) of the GalNAc glycopeptides. T glycoforms were produced by a recombinant *Drosophila* core1  $\beta$ 3galactosyltransferase, truncated core3 glycoforms (structure no. 6, Table I) were produced with a recombinant human  $\beta$ 3GlcNAc-transferase (Iwai et al. 2002), and non-capped type1-core3 glycoforms (structure no. 9, Table I) were produced using  $\beta$ 3Gal-T5 (see, U.S. Pat. No. 7,332,279).

Recombinant enzymes were expressed in insect cells using the baculo-virus system and used after semi-purification by Ni-chromatography (when HIS-tagged) or by ion exchange chromatographies. Glycosylation was monitored by staining of slides with lectins (HPA, VVA) (Sigma) and monoclonal antibodies to Tn (HBTn1, HBSTn1, HBT1) (Dako, Denmark). On-slide glycosylation was performed as follows: slides were quenched for 1 hr in 50 mM ethanolamine in 100 mM sodium borate pH 8, washed extensively in de-ionized water, and spun dry. Slides were blocked for 1 h with 1% BSA in PBS, pH 7.4, and in some cases with NP40 (1%) to reduce background. Slides were washed in PBS/0.05% Tween and enzyme reaction mixtures with BSA and detergent were applied and incubated 1-2 hrs at 37° C. Reaction mixtures for polypeptide GalNAc-transferases included MES buffer 125 mM, pH 7.4, 1% NP40, 1% BSA, 250  $\mu$ M UDP-GalNAc, 2 mM MnCl<sub>2</sub> and 20  $\mu$ g/mL enzyme. Reaction mixtures for galactosyltransferases included UDP-Gal, sialyltransferases CMP-NeuAc, GlcNAc-transferases UDP-GlcNAc. Following on-slide glycosylation slides were washed with PBS/Tween and processed with antibodies and lectins as described below.

It will be clear to one of ordinary skill in the art that on-slide glycosylation serves as a method to screen for additional glycoforms of peptides which may be recognized by auto-antibodies present in patients. Once a particular glycoform of a given peptide is found to react with an autoantibody from a patient, the glycopeptide can be resynthesized in solution using the same enzymes used for on-slide glycosylation and the glycan structure and sites of attachment in the peptide confirmed by mass spectrometry (Tarp et al. 2007). The validated glycopeptide can then be incorporated into diagnostic panels as described throughout the specification and in Example 4.

FIG. 1 illustrates an example of on-slide glycosylation with the polypeptide GalNAc-transferase, GalNAc-T3, to glycosylate peptides and GalNAc glycopeptides having additional unsubstituted Ser/Thr residues to enhance the number of O-glycans. A library of 96 paired GalNAc-glycopeptides/peptides (20-mers with and without a single GalNAc residue at position 12), as designated in Table II, supra, were printed in triplicates (horizontal) on Scieon 16-well slides by JPT (Germany). In each pair in Table II, the glycopeptide of the pair contains a bold, underlined amino acid residue, indicating the site of attachment of GalNAc. Peptide pairs by peptide number are as follows: 1/2, 3/4, 5/6 . . . etc. The slide was reacted with the anti-Tn lectin HPA (1  $\mu$ g/ml) without (FIG. 1A) and with (FIG. 1B) prior treatment with recombinant polypeptide GalNAc-T3 enzyme for on-slide GalNAc-glycosylation of available unglycosylated sites on peptides and glycopeptides.

The HPA lectin did not react with all GalNAc-glycopeptides (e.g., glycopeptide nos. 1-5 and 25-29), which is partly due to failure in synthesis and/or printing at these positions, as well as some restrictions of specificity of the GalNAc-binding lectin. The GalNAc-glycopeptides 1-5 did react with the HPA lectin in other experiments, and it was therefore concluded that there was a print failure. Conversion of peptides to GalNAc-glycopeptides by on-slide reaction with a polypeptide GalNAc-transferase is also expected to be dependent on the substrate specificity of the enzyme used, and, e.g., use of GalNAc-T2 rather than T3 may give a partly different labeling pattern.

Regardless, it is evident that most of the GalNAc-glycopeptides were labeled with HPA (FIG. 1A) and that most of the corresponding paired peptides were labeled only after GalNAc-T3 on-slide glycosylation (FIG. 1B). While HPA may not be expected to react with all GalNAc-glycopeptides, this lectin and other Tn reactive lectins such as HAA, VVA and DBA, as well as monoclonal anti-Tn antibodies (Dako) provide excellent controls for determining the quality of peptide synthesis and printing.

#### Example 2

##### High Through-Put Screening of Glycopeptide Microarrays with Human Serum for Identification of Glycopeptides Recognized by Cancer-Associated Auto-Antibodies

###### Sera Origin and Handling:

A panel of human sera was obtained from CHTN (Cooperative Human Tissue Network) and Asterand Inc., under the guidelines of approved agreements by the providers. Sera obtained were from control individuals ("normal") (n=31) and from newly diagnosed cancer patients (n=147) with pancreatic, breast, colon, lung, prostate or ovary primary cancers. Briefly, for cancer sera, all blood samples were obtained on or near date of diagnosis, and serum was processed immediately, flash frozen and stored at -70° C. until shipment. Serum samples received from the providers as frozen aliquots generally of 1-2 mL were brought to room temperature, vortexed and distributed into 20-100  $\mu$ L aliquots in closeable Eppendorf tubes (vWR) (pre-labeled), and immediately frozen and stored at -70° C. until use.

###### Glycopeptide Microarray Method:

Glycopeptides (20-mers with and without a single GalNAc residue at position 12) and control structures (corresponding unglycosylated peptides) were printed on Corning (Corning, N.Y.), Scieon (Germany) or Schott Nexterion® Slide H or Schott Nexterion® Slide H MPX 16 (Schott AG, Mainz,

Germany) by JPT (Germany). Triplicates or quadruplicates of all compounds were printed at optimal concentrations (1-50  $\mu$ M) or 50 $\times$  excess relative to scale of synthesis for spot-synthesized glycopeptides printed without purification. After printing, slides were incubated for 1 hour (h) in a humidified hybridization chamber with 70-100% relative humidity and stored until use at 4 $^{\circ}$  C. Unspotted slide areas were blocked for 1 h with 25 mM ethanolamine in 100 mM sodium borate pH 8.5. If an enzyme step was needed either to increase sites of GalNAc attachments in peptides or extend O-glycans to T, STn, core 3 or other structures, addition of the enzyme reaction mixture in 25-35  $\mu$ L was made in appropriate wells and the slide incubated at 37 $^{\circ}$  C. for 1 h, after which it was washed in PBS/0.05% Tween and then PBS, and then spun dry.

Human sera (usually diluted 1:25), monoclonal antibodies, lectins and the like were added in 25  $\mu$ L and the slide left at room temperature for 2 h in a moist, humid chamber after which it was washed as above and spun dry (if no superstructure). Secondary antibodies were added at appropriate concentrations (for human sera, usually 1:1500 for anti-human IgG with a Cy3 chromophore). In some cases, for some controls, lectin-Cy3 was used directly as final step. The final step was washing as above, with a brief de-ionized water wash and the slide spun dry for scanning Analysis was made on a GenePix 4200AL Scanner at PMT 400 and power mode 10-50. Data were analyzed and plotted using Microsoft Excel.

Identification of Cancer-Associated Auto-Antibodies to GalNAc-Glycopeptide Epitopes:

Glycopeptides (20-mers with and without a single GalNAc residue at position 12) were printed in triplicates (horizontal) on Scineon 16-well slides by JPT (Germany) and bound human IgG antibodies detected by a labeled secondary anti-human IgG antibody. FIG. 2 illustrates examples of reactivities of serum (1:25 dilution) from a newly diagnosed prostate cancer patient (#762 in Panel A) and a normal control serum from a healthy individual (#174 in Panel B) on the library of 96 paired peptides/GalNAc-glycopeptides as designated in Table II. Candidate cancer-associated IgG antibodies identified in the cancer serum directed to GalNAc glycopeptide epitopes are indicated by open circles labeled 20/21, 62/63, and 86/87 for the paired peptide and GalNAc glycopeptides, respectively. The analysis demonstrates that serum of cancer patient contain IgG antibodies specifically reacting with epitopes found on GalNAc glycopeptides 21, 63, and 87, and since these antibodies do not react with the corresponding unglycosylated peptides 20, 62, and 86, it may be concluded that the epitopes are comprised of a GalNAc-peptide epitope including both the O-glycan part as well as part of the peptide sequence.

Human IgG antibodies from several cancers were shown to bind selectively to several GalNAc-glycopeptides and not the corresponding peptide, and such antibodies were not detected in healthy individuals. An example of this is shown in FIG. 2, where a prostate cancer serum (prca#762) labels three GalNAc-glycopeptides (#21, 63, and 87), and not the corresponding peptide (#20, 62, and 86). These three candidates were also identified in other cancer sera but not in the controls as shown in FIGS. 3-5, and described, *infra*.

FIG. 3 illustrates results of screening 147 cancer sera and 31 control sera (normal sera) on the glycopeptide pair #20/21. Sera obtained from newly diagnosed cancer patients with lung, colon, ovary, prostate, pancreas or breast tumors as well as controls (as indicated) were reacted with the 96-peptide array on Scineon 16-well slides (1:25 dilution) followed by cy3 labeled anti-human IgG (diluted to 1:1500). Arrays were

analyzed on GenePix 4200 scanner at 400 pmt with 50 power and relative intensities graphed.

FIG. 4 illustrates results of screening 147 cancer sera and 31 normal sera on the glycopeptide pair #62/63. FIG. 5 illustrates results of screening 147 cancer sera and 31 normal sera on the glycopeptide pair #86/87.

Peptides 20/21, each having the sequence identified as SEQ ID NO: 15, are derived from SPP1 (Ensg00000118785) GenBank Accession No. NP\_001035147 (SEQ ID NO: 61), peptides 62/63, each having the sequence identified as SEQ ID NO: 36 are derived from LAMP2 (Ensg00000005893) (ENST00000200639) protein (ENSP00000200639) GenBank Accession No. NP\_002285 (SEQ ID NO: 64), and peptides 86/87, each having the sequence identified as SEQ ID NO: 49, are derived from KLK1 (gene: Ensg00000167748) (transcript: ENST00000301420) (protein: ENSP00000301420) (GenBank Accession No. NP\_002248) (SEQ ID NO: 66). These proteins have broad expression patterns in tissues and hence may induce antibodies in many cancers.

The presented method using a limited glycopeptide library identified three candidate targets for human disease-associated auto-antibodies. These auto-antibody targets were defined by the discriminating factor that cancer-associated IgG antibodies reacted selectively with a glycopeptide and not the corresponding peptide or other glycopeptides with the same O-glycan or the O-glycan presented as a hapten on an artificial carrier.

### Example 3

#### Generation of Antibodies to Identified Auto-Antibody Targets for Diagnostic Use

Monoclonal or polyclonal antibodies may be generated to the identified glycopeptide antigens by known methods (Takeuchi et al. 2002; Hanisch et al. 1995; Reis et al. 1998; Sorensen et al. 2006). Briefly, the following procedure serves as an example for generation of antibodies with the desired glycopeptides specificity but other procedures leading to the same result will be known to the skilled in the art.

##### Immunization Protocol:

Glycopeptides are coupled to keyhole limpet hemocyanin (KLH) (Pierce, Rockford, Ill.) using glutaraldehyde. Efficiency of conjugation is assessed by analyzing the reaction by size exclusion chromatography on a PD-10 column, where the conjugate/glycopeptides ratio can be determined by ELISA using appropriate reagents such as antibodies and lectins detecting the glycopeptides. Essentially all reactivity with a Tn reactive lectin (HPA) is found with the excluded fraction and insignificant reactivity in the included fractions expected to contain peptides. Titration analysis of the KLH conjugate with the corresponding glycopeptide in ELISA indicated conjugation ratio KLH to glycopeptide of approximately 1:200. Female Balb/c (Jackson Labs) wild type mice are injected subcutaneously with 10 or 15  $\mu$ g of glycopeptide-KLH in a total volume of 200  $\mu$ l (1:1 mix with Freund's adjuvant, Sigma). Mice received four immunizations 2-4 wks apart, and blood samples are obtained by tail or eye bleeding 1 wk following the third and fourth immunization.

##### Hybridoma Production:

Mouse hybridomas are produced by fusion of splenocytes to NS-1 followed by selection in HAT/HT (Hypoxanthine, Aminopterin, Thymidine). Hybridomas are selected by initial screening by ELISA with GalNAc-glycopeptides and corresponding peptides as well as irrelevant control compounds. Further characterization is done on glycopeptides microar-

rays as well as on a panel of human cancer cell lines expressing the corresponding aberrant glycoprotein.

Enzyme-linked immunosorbent assays (ELISA) are performed using 96-well MaxiSorp™ plates (Nunc). Plates are coated overnight at 4° C. with 1 µg/ml of glycopeptides in bicarbonate-carbonate buffer (pH 9.5), blocked with 5% BSA in PBS, followed by incubation with sera (diluted in PBS) or monoclonal antibodies for 2 hours (hrs) at room temperature. Bound antibodies are detected with peroxidase-conjugated rabbit anti-mouse immunoglobulins (Dako, Denmark) or isotype specific antibodies peroxidase-conjugated goat anti-mouse IgM, IgG1, IgG2a, IgG2b, or IgG3 (Southern Biotechnology Associates, USA). Plates are developed with o-phenylenediamine tablets (Dako, Denmark) and read at 492 nm. Control antibodies included anti-carbohydrate antibodies HBTn-1 (Tn) and HBSTn-1 (STn) (Dako) and lectins HPA, VVA and HAA (Sigma). Control sera included mice immunized with irrelevant peptides linked to KLH. Human cancer cell lines from different cancers are all obtained from ATCC and cultured as recommended by ATCC.

Immunocytochemical staining of cells are performed as follows: cells are harvested by trypsination, washed and plated onto multi-well glass slides and fixed for 10 minutes (min) in ice cold acetone or in methanol acetone. Fixed cells are incubated overnight at 4° C. with mouse sera (1:200/1:400/1:800) or hybridoma antibodies, followed by incubation for 45 min at room temperature with FITC-conjugated rabbit anti-mouse immunoglobulins (Dako, Denmark). Slides are mounted in glycerol containing p-phenylenediamine and examined in a fluorescence microscope.

For further determination of expression of glycopeptides epitope in human cancers immunohistochemistry of fixed and frozen tissue samples are performed. Frozen sections are fixed for 10 min in cold methanol/acetone (50:50). Formalin fixed, paraffin wax embedded tissues of different carcinoma and healthy tissues are obtained from Origine (US) and stained by immunofluorescence or peroxidase techniques. Paraffin sections are dewaxed, rehydrated, and treated with 0.5% H<sub>2</sub>O<sub>2</sub> in methanol for 30 min. Section are rinsed in TBS

and incubated for 20 min with rabbit nonimmune serum. Sections are rinsed and incubated overnight at 4° C. with primary antibody. Sections are rinsed and incubated with biotin-labeled rabbit anti-mouse serum (Dako, Denmark) diluted 1:200 in TBS for 30 min, rinsed with TBS, and incubated for 1 h with avidin-biotin-peroxidase complex (Dako, Denmark). Sections are rinsed with TBS and developed with 0.05% 3,3'-diaminobenzidine tetrahydrochloride freshly prepared in 0.05 M TBS containing 0.1% H<sub>2</sub>O<sub>2</sub>. Sections are stained with hematoxylin, dehydrated and mounted.

#### Example 4

##### Broad Discovery of O-Glycopeptide Epitopes

A larger library of GalNAc O-glycopeptides designed with GalNAc linked to serine or threonine at position 12 in 20-mer peptides was produced as described in Example 1. Peptides were selected among cell membrane and secreted human proteins that contain serine and threonine residues that are predicted to be O-glycosylated by the NetOGlyc algorithm (Julenius et al. 2005). A total of 960 GalNAc glycopeptides were synthesized at 0.5 mg scale (Sigma) and printed on microarray hydrogel slides (Schott Nexterion) as described in Example 1. Slides were reacted with human cancer sera (ovarian, breast, colon, lung, pancreas, prostate, 235 total sera) and control sera (145 healthy, 20 inflammatory, 20 benign tumor). Glycopeptides preferentially reactive with human IgG antibodies from cancer patients compared to controls were selected for resynthesis at 5 mg scale with amidated C-terminus (New England Peptide (Gardner, Mass.) (Table III). Resynthesized glycopeptides were reprinted on microarray slides at 50 µM and reacted with human cancer sera (Total 286 sera: 32 ovarian cancer (O), 38 breast cancer (B), 54 colon cancer (C), 17 lung cancer (L), and 145 age and sex matched control normal sera as described in Example 1. Table III lists glycopeptides exclusively or preferentially reactive with human IgG from cancer patients compared to controls and examples of reactivities are shown in FIG. 6.

TABLE III

Glycopeptides reactive with IgG antibodies from human cancer sera			
Peptide number	Sequence ID	Protein	Sequence
166	82	Oncostatin	H2N-TKAGRGASQPPTPTPASDAF-amide
113	83	gp95	H2N-EEEEETAEDTTEDETEQDED-amide
218	84	MUC13	H2N-TASTTANTPFPTATSPAPPI-amide
225	85	MUC13	H2N-PAPPIISTHSSSTIPTAPP-amide
<b>275a</b>	86	Ceruplasm	H2N-LAKMYYSAVEPTKDIFTGLI-amide
284	87	CD46	H2N-PSSTKPPALSHSVSTSSSTK-amide
308	88	EBAG9	H2N-LEPDYFKDMTPTIRKTQKIV-amide
318a	89	MUC17	H2N-STMPVVSSEASTHSTTPVDT-amide
324	90	MUC17	H2N-STHSTTPVDTSTPVTSTEA-amide
370	91	IL6-R	H2N-IPPEDTASTRSSFTVQDLKP-amide
382	92	R-PTP-alpha	H2N-EAKTSNPTSSLTSLSVAPTF-amide
389	93	R-PTP-alpha	H2N-ARTEPWEGNSSTAATTPETF-amide
443	94	ODAM	H2N-VDPLQLQTPPQTQPGPSHVM-amide
450	95	ODAM	H2N-SPKPSTTNVFTSAVDQTITP-amide
456	96	IGFB-3	H2N-PAPPAPGNASESEEDRSAGS-amide
458	97	IGFB-3	H2N-ASESEEDRSAGSVESPSVSS-amide
465	98	MUC15	H2N-ANLNSDKENITTSNLKASHS-amide
484	99	MUC15	H2N-LTTNSDSFTGFTPYQEKTTL-amide
485	100	MUC15	H2N-SFTGFTPYQEKTTLQPTLKF-amide
485a	101	MUC15	H2N-SFTGFTPYQEKTTLQPTLKF-amide
505	102	TPBG Trophob	H2N-SPTSSASSFSSAPFLASAV-amide
522	103	IgA1 hinge	H2N-TVPCPVPSTPPTPSPSTPPT-amide
524	104	IgA1 hinge	H2N-VPSTPPTPSPSTPPTPSPSC-amide
544	105	R-PTP-N	H2N-SEPPKAARPPVTPVLEKKS-amide
546	106	R-PTP-N	H2N-GQSQPTVAGQPSARPAEEY-amide

TABLE III-continued

Glycopeptides reactive with IgG antibodies from human cancer sera			
Peptide number	Sequence ID	Protein	Sequence
558	107	CMRF35	H2N-TPASITAAKTSTITTAFFPV-amide
569	108	TNF-RSF1B	H2N-GNASMDAVCTSTSPTRSMAP-amide
<b>585</b>	109	CGB2	H2N-TDCGGPKDHPLTCDDPRFQA-amide
587	110	CGB2	H2N-AQASSSSKAPPPSLPSPRLP-amide
592	111	Acrosomal SP Cadherin 1	H2N-PLSELESGEQPSDEQPSGEH-amide
601	112	(CD)	H2N-PQRSSTAILQVSVTDTNDNH-amide
605	113	CD Ovomorolin	H2N-GALPGTSVMEVTATDADDDV-amide
612	114	CD Mucin like	H2N-EQEPSTDVPPSPEAGGTTG-amide
676	115	Inhibin alpha	H2N-RPEATPFLVAHTRTRPPSGG-amide
<b>690</b>	116	IGF-BP-6	H2N-PGTSTTPSQNSAGVQDTEM-amide
739	117	LTBP1	H2N-EVAPEASTSSASQVIAPTQV-amide
752	118	CD 248 Endosialin	H2N-QPPDFALAYRPSFPEDREPQ-amide
755	119	CD 248 Endosialin	H2N-LSVTRPVVVSATHPTLPSAH-amide
757	120	CD 248 Endosialin	H2N-PSAHQPPVIPATHPALSRDH-amide
765	121	CD 248 Endosialin	H2N-APDALVLRQTATQLPIIPTA-amide
823	122	ICAM-1	H2N-GALFPGPGNAQTSVSPSKI-amide
827	123	ICAM-1	H2N-HLALGDQRLNPTVTYGNDSF-amide
827a	124	ICAM-1	H2N-HLALGDQRLNPTVTYGNDSF-amide
848	125	MUC1	H2N-PATEPASGSAATWGQDVTSV-amide
852	126	MUC1	H2N-VPVTRPALGSTTPPAHDVTS-amide
859	127	MUC1	H2N-NVTSASGSASGSASTLVHNG-amide
859a	128	MUC1	H2N-NVTSASGSASGSASTLVHNG-amide
863	129	MUC1	H2N-GTSARATTPASKSTPFSIP-amide
863a	130	MUC1	H2N-GTSARATTPASKSTPFSIP-amide
870	131	MUC1	H2N-SDTPTTLASHSTKTDASSTH-amide
<b>873</b>	132	MUC1	H2N-TKTDASSTHHSTVPLTSSN-amide
883	133	MUC1	H2N-TDYQELQRDISEMFLQIYK-amide
<b>889</b>	134	MUC1	H2N-HDVETQFNQYKTEAASRYNL-amide
<b>893</b>	135	MUC1	H2N-ASRYNLTISDVSVDVPPFSA-amide
894	136	MUC1	H2N-RYNLTISDVSVDVPPFSA-amide
895	137	MUC1	H2N-DVSVSDVPPFSAQSGAGVP-amide
914	138	MUC4	H2N-TAGRPTGQSSPTSPASPQE-amide
931	139	MUC4	H2N-SLASQATDIFSTVPPTPPSI-amide
934	140	MUC4	H2N-FSTVPPTPPSITSTGLTSPQ-amide
936	141	MUC4	H2N-PTPPSITSTGLTSPQTETHT-amide
941	142	MUC4	H2N-LTSPQTETHTLSPSGGKTF-amide
977	143	MUC4	H2N-TDTSSASTGHATPLPVTSLS-amide
983	144	MUC4	H2N-HATPLAVSSATSASTVSSDS-amide
<b>852-C3</b>	145	MUC1	<u>H2N-</u> <u>VPVTRPALGSTT[GlcNAc]PPAHDVTS-</u> <u>amide</u>
<b>931-C3</b>	146	MUC4	<u>H2N-</u> <u>SLASQATDIFST[GlcNAc]VPPTPPSI-</u> <u>amide</u>

\*Bold S or T indicates attachment site of GalNAc residues to Ser/Thr; Bold [GlcNAc] indicates an addition of glucosamine attached to GalNAc (in bold). Bold, underlined name indicates peptide assayed in graphs in FIG. 6.

Since IgG antibodies reactive with glycopeptides epitopes recognize both the peptide sequence in close proximity to the O-glycan (i.e., one to five or even eighth residues N- and C-terminal of the O-glycan) as well as the O-glycan structure, it is clear that different glycoforms of one glycopeptide may be recognized by different IgG antibodies and these antibodies may be found in different cancer patients. In this Example, GalNAc-glycopeptides from MUC1 and MUC4 were also produced as the core 3 GlcNAc $\beta$ 1-3GalNAc $\alpha$ 1-O-Ser/Thr glycoform with a recombinant core 3 synthase as described in Example 1. Two core 3 glycopeptides (#852-C3 and #931-C3) were identified as exclusively recognized by IgG antibodies in sera from cancer patients.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from

the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

It is further to be understood that all values are approximate, and are provided for description.

Patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

#### LITERATURE CITED

- Anderson K S, Labaer J (2005) The sentinel within: exploiting the immune system for cancer biomarkers. *J Proteome Res* 4:1123-1133.
- Anderson K S, Ramachandran N, Wong J, Raphael J V, Hainsworth E, Demirkan G, Cramer D, Aronzon D, Hodi F S, Harris L, Logvinenko T, Labaer J (2008) Application of

- protein microarrays for multiplexed detection of antibodies to tumor antigens in breast cancer. *J Proteome Res* 7:1490-1499.
- Anderton S M (2004) Post-translational modifications of self antigens: implications for autoimmunity. *Curr Opin Immunol* 16:753-758.
- Backlund J, Treschow A, Bockermann R, Holm B, Holm L, Issazadeh-Navikas S, Kihlberg J, Holmdahl R (2002) Glycosylation of type II collagen is of major importance for T cell tolerance and pathology in collagen-induced arthritis. *Eur J Immunol* 32:3776-3784.
- Bennett E P, Hassan H, Clausen H (1996) cDNA cloning and expression of a novel human UDP-N-acetyl-alpha-D-galactosamine-Polypeptide N-acetylgalactosaminyltransferase, GalNAc-T3. *Journal of Biological Chemistry* 271:17006-17012.
- Bennett E P, Hassan H, Mandel U, Mirgorodskaya E, Roepstorff P, Burchell J, Taylor-Papadimitriou J, Hollingsworth M A, Merckx G, van Kessel A G, Eiberg H, Steffensen R, Clausen H (1998) Cloning of a human UDP-N-acetyl-alpha-D-Galactosamine:polypeptide N-acetylgalactosaminyltransferase that complements other GalNAc-transferases in complete O-glycosylation of the MUC1 tandem repeat. *J Biol Chem* 273:30472-30481.
- Brandlein S, Eck M, Strobel P, Wozniak E, Muller-Hermelink H K, Hensel F, Vollmers H P (2004a) PAM-1, a natural human IgM antibody as new tool for detection of breast and prostate precursors. *Hum Antibodies* 13:97-104.
- Brandlein S, Pohle T, Vollmers C, Wozniak E, Ruoff N, Muller-Hermelink H K, Vollmers H P (2004b) CFR-1 receptor as target for tumor-specific apoptosis induced by the natural human monoclonal antibody PAM-1. *Oncol Rep* 11:777-784.
- Chapman C, Murray A, Chakrabarti J, Thorpe A, Woolston C, Sahin U, Barnes A, Robertson J (2007) Autoantibodies in breast cancer: their use as an aid to early diagnosis. *Ann Oncol* 18:868-873.
- Clark R A, Fuhlbrigge R C, Springer T A (1998) L-Selectin ligands that are O-glycoprotease resistant and distinct from MECA-79 antigen are sufficient for tethering and rolling of lymphocytes on human high endothelial venules. *J Cell Biol* 140:721-731.
- Danielczyk A, Stahn R, Faulstich D, Loffler A, Marten A, Karsten U, Goletz S (2006) PankoMab: a potent new generation anti-tumour MUC1 antibody. *Cancer Immunol Immunother* 55:1337-1347.
- Dian D, Janni W, Kuhn C, Mayr D, Karsten U, Mylonas I, Friese K, Jeschke U (2009) Evaluation of a novel anti-mucin 1 (MUC1) antibody (PankoMab) as a potential diagnostic tool in human ductal breast cancer; comparison with two established antibodies. *Onkologie* 32:238-244.
- Doyle H A, Mamula M J (2001) Post-translational protein modifications in antigen recognition and autoimmunity. *Trends Immunol* 22:443-449.
- Doyle H A, Mamula M J (2005) Posttranslational modifications of self-antigens *Ann NY Acad Sci* 1050:1-9.
- Gahring L, Carlson N G, Meyer E L, Rogers S W (2001) Granzyme B proteolysis of a neuronal glutamate receptor generates an autoantigen and is modulated by glycosylation. *J Immunol* 166:1433-1438.
- Hanisch F G, Stadie T, Bosslet K (1995) Monoclonal-Antibody Bw835 Defines A Site-Specific Thomsen-Friedenreich Disaccharide Linked to Threonine Within the Vtsa Motif of Muc1 Tandem Repeats. *Cancer Research* 55:4036-4040

- Hassan H, Bennett E P, Mandel U, Hollingsworth M A, Clausen H (2000) Carbohydrates in Chemistry and Biology—a Comprehension Handbook. Wiley-VCH, pp. 273-292.
- Hellstrom I, Friedman E, Verch T, Yang Y, Korach J, Jaffar J, Swisher E, Zhang B, Ben Baruch G, Tan M C, Goedegebuure P, Hellstrom K E (2008) Anti-mesothelin antibodies and circulating mesothelin relate to the clinical state in ovarian cancer patients. *Cancer Epidemiol Biomarkers Prev* 17:1520-1526.
- Iwai T, Inaba N, Naundorf A, Zhang Y, Gotoh M, Iwasaki H, Kudo T, Togayachi A, Ishizuka Y, Nakanishi H, Narimatsu H (2002) Molecular cloning and characterization of a novel UDP-GlcNAc:GalNAc-peptide beta1,3-N-acetylglucosaminyltransferase (beta 3Gn-T6), an enzyme synthesizing the core 3 structure of O-glycans. *J Biol Chem* 277:12802-12809.
- Julenius K, Molgaard A, Gupta R, Brunak S (2005) Prediction, conservation analysis, and structural characterization of mammalian mucin-type O-glycosylation sites. *Glycobiology* 15:153-164.
- Kawabata R, Wada H, Isobe M, Saika T, Sato S, Uenaka A, Miyata H, Yasuda T, Doki Y, Noguchi Y, Kumon H, Tsuji K, Iwatsuki K, Shiku H, Ritter G, Murphy R, Hoffman E, Old L J, Monden M, Nakayama E (2007) Antibody response against NY-ESO-1 in CHP-NY-ESO-1 vaccinated patients. *Int J Cancer* 120:2178-2184.
- Li J, Sullivan C A, Harris L (2009) Where do we place PankoMab in the reagents used to study the MUC1 superfamily? *Onkologie* 32:235-237
- Liu W L, Zhang G, Wang J Y, Cao J Y, Guo X Z, Xu L H, Li M Z, Song L B, Huang W L, Zeng M S (2008) Proteomics-based identification of autoantibody against CDC25B as a novel serum marker in esophageal squamous cell carcinoma. *Biochem Biophys Res Commun* 375:440-445.
- Lu H, Goodell V, Disis M L (2008) Humoral immunity directed against tumor-associated antigens as potential biomarkers for the early diagnosis of cancer. *J Proteome Res* 7:1388-1394.
- Lubin R, Schlichtholz B, Bengoufa D, Zalcman G, Tredaniel J, Hirsch A, de Fromental C C, Preudhomme C, Fenaux P, Fournier G, Mangin P, Laurent-Puig P, Pelletier G, Schlumberger M, Desgrandchamps F, Le Duc A, Peyrat J P, Janin N, Bressac B, Soussi T. (1993) Analysis of p53 antibodies in patients with various cancers define B-cell epitopes of human p53: distribution on primary structure and exposure on protein surface. *Cancer Res* 53:5872-5876.
- Mintz P J, Kim J, Do K A, Wang X, Zinner R G, Cristofanilli M, Arap M A, Hong W K, Troncoso P, Logothetis C J, Pasqualini R, Arap W (2003) Fingerprinting the circulating repertoire of antibodies from cancer patients. *Nat Biotechnol* 21:57-63.
- Pereira-Faca S R, Kuick R, Purays E, Zhang Q, Krasnoselsky A L, Phanstiel D, Qiu J, Misek D E, Hinderer R, Tammemagi M, Landi M T, Caporaso N, Pfeiffer R, Edelstein C, Goodman G, Barnett M, Thornquist M, Brenner D, Hanash S M (2007) Identification of 14-3-3 theta as an antigen that induces a humoral response in lung cancer. *Cancer Res* 67:12000-12006.
- Ramachandran N, Raphael J V, Hainsworth E, Demirkan G, Fuentes M G, Rolfs A, Hu Y, Labaer J (2008) Next-generation high-density self-assembling functional protein arrays. *Nat Methods* 5:535-538.

- Rasmussen N, Ditzel H J (2009) Identification of the specificity of isolated phage display single-chain antibodies using yeast two-hybrid screens. *Methods Mol Biol* 562: 165-176.
- Rauschert N, Brandlein S, Holzinger E, Hensel F, Muller-Hermelink H K, Vollmers H P (2008) A new tumor-specific variant of GRP78 as target for antibody-based therapy. *Lab Invest* 88:375-386.
- Reis C A, Sorensen T, Mandel U, David L, Mirgorodskaya E, Roepstorff P, Kihlberg J, Hansen J E, Clausen H (1998) Development and characterization of an antibody directed to an alpha-N-acetyl-D-galactosamine glycosylated MUC2 peptide. *Glycoconj J* 15:51-62.
- Sabbatini P J, Ragupathi G, Hood C, Aghajanian C A, Juretzka M, Iasonos A, Hensley M L, Spassova M K, Ouerfelli O, Spriggs D R, Tew W P, Konner J, Clausen H, Abu R N, Dansiefsky S J, Livingston P O (2007) Pilot study of a heptavalent vaccine-keyhole limpet hemocyanin conjugate plus QS21 in patients with epithelial ovarian, fallopian tube, or peritoneal cancer. *Clin Cancer Res* 13:4170-4177.
- Sahin U, Tureci O, Schmitt H, Cochlovius B, Johannes T, Schmits R, Stenner F, Luo G, Schobert I, Pfreundschuh M (1995) Human neoplasms elicit multiple specific immune responses in the autologous host. *Proc Natl Acad Sci USA* 92:11810-11813.
- Schietinger A, Philip M, Yoshida B A, Azadi P, Liu H, Meredith S C, Schreiber H (2006) A mutant chaperone converts a wild-type protein into a tumor-specific antigen. *Science* 314:304-308.
- Snijdwint F G M, Mensdorff-Pouilly S, Karuntu-Wanamarta A H, Verstraeten A A, Zanten-Przybysz I, Hummel P, Nijman H W, Kenemans P, Hilgers J (1999) Cellular and humoral immune responses to MUC1 mucin and tandem-repeat peptides in ovarian cancer patients and controls. *Cancer Immunology Immunotherapy* 48:47-55.

- Sorensen A L, Reis C A, Tarp M A, Mandel U, Ramachandran K, Sankaranarayanan V, Schwientek T, Graham R, Taylor-Papadimitriou J, Hollingsworth M A, Burchell J, Clausen H (2006) Chemoenzymatically synthesized multimeric Tn/STn MUC1 glycopeptides elicit cancer-specific anti-MUC1 antibody responses and override tolerance. *Glycobiology* 16:96-107.
- Springer G F (1984) T and Tn, General Carcinoma Auto-Antigens. *Science* 224:1198-1206.
- Springer G F, Tegtmeier H (1980) On the origin of anti-Thomsen-Friedenreich (T) antibodies. *Naturwissenschaften* 67:317-318.
- Stockert E, Jager E, Chen Y T, Scanlan M J, Gout I, Karbach J, Arand M, Knuth A, Old L J (1998) A survey of the humoral immune response of cancer patients to a panel of human tumor antigens. *J Exp Med* 187:1349-1354.
- Takeuchi H, Kato K, Denda-Nagai K, Hanisch F G, Clausen H, Irimura T (2002) The epitope recognized by the unique anti-MUC1 monoclonal antibody MY.1E12 involves sialyl alpha 2-3galactosyl beta 1-3N-acetylgalactosaminide linked to a distinct threonine residue in the MUC1 tandem repeat. *Journal of Immunological Methods* 270:199-209.
- Tarp M A, Clausen H (2008) Mucin-type O-glycosylation and its potential use in drug and vaccine development. *Biochim Biophys Acta* 1780:546-563.
- Tarp M A, Sorensen A L, Mandel U, Paulsen H, Burchell J, Taylor-Papadimitriou J, Clausen H (2007) Identification of a novel cancer-specific immunodominant glycopeptide epitope in the MUC1 tandem repeat. *Glycobiology* 17:197-209.
- Vollmers H P, Brandlein S (2009) Natural antibodies and cancer. *N Biotechnol* 25:294-298.
- White T, Bennett E P, Takio K, Sorensen T, Bonding N, Clausen H (1995) Purification and cDNA cloning of a human UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase. *J Biol Chem* 270: 24156-24165.

## SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 146

<210> SEQ ID NO 1

<211> LENGTH: 273

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr  
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
35 40 45

Thr Glu Lys Asn Ala Leu Ser Thr Gly Val Ser Phe Phe Phe Leu Ser  
50 55 60

Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp Pro Ser  
65 70 75 80

Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu  
85 90 95

Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe  
100 105 110

Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly

-continued

115	120	125
Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr 130 135 140		
Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser 145 150 155 160		
Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly 165 170 175		
Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala 180 185 190		
Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn 195 200 205		
Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met 210 215 220		
Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser 225 230 235 240		
Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly 245 250 255		
Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn 260 265 270		

Leu

&lt;210&gt; SEQ ID NO 2

&lt;211&gt; LENGTH: 264

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 2

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr 1 5 10 15
Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly 20 25 30
Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala 35 40 45
Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Phe Asn 50 55 60
Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg 65 70 75 80
Asp Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu 85 90 95
Gly Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu 100 105 110
Thr Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr 115 120 125
Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr 130 135 140
Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln 145 150 155 160
Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val 165 170 175
Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val 180 185 190
Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala 195 200 205
Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His

-continued

```

210                215                220
Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys
225                230                235                240
Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala
245                250                255
Val Ala Ala Thr Ser Ala Asn Leu
260

```

```

<210> SEQ ID NO 3
<211> LENGTH: 255
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 3

```

```

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1                5                10                15
Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
20                25                30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35                40                45
Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp
50                55                60
Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile
65                70                75                80
Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro
85                90                95
Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile
100               105               110
Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala
115               120               125
Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val
130               135               140
Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly
145               150               155               160
Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val
165               170               175
Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly
180               185               190
Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu
195               200               205
Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr
210               215               220
Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser
225               230               235               240
Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu
245               250               255

```

```

<210> SEQ ID NO 4
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptides

```

```

<400> SEQUENCE: 4

```

```

Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro
1                5                10                15

```



-continued

Ala His Gly Val  
20

<210> SEQ ID NO 5  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 5

Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala  
1 5 10 15

His Gly Val Thr  
20

<210> SEQ ID NO 6  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 6

Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp  
1 5 10 15

Thr Arg Pro Ala  
20

<210> SEQ ID NO 7  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 7

Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
1 5 10 15

Arg Pro Ala Pro  
20

<210> SEQ ID NO 8  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 8

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
1 5 10 15

Gly Ser Thr Ala  
20

<210> SEQ ID NO 9  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 9

Phe Tyr Leu Ala Met Pro Phe Ala Thr Pro Met Glu Ala Glu Leu Ala

-continued

---

1                    5                    10                    15

Arg Arg Ser Leu  
                  20

<210> SEQ ID NO 10  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 10

Lys Phe Ser Glu Phe Trp Asp Leu Asp Pro Glu Val Arg Pro Thr Ser  
1                    5                    10                    15

Ala Val Ala Ala  
                  20

<210> SEQ ID NO 11  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 11

Pro Leu Val Glu Gln Gly Arg Val Arg Ala Ala Thr Val Gly Ser Leu  
1                    5                    10                    15

Ala Gly Gln Pro  
                  20

<210> SEQ ID NO 12  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 12

Leu Trp Ser Leu Cys Trp Ser Leu Ala Ile Ala Thr Pro Leu Pro Pro  
1                    5                    10                    15

Thr Ser Ala His  
                  20

<210> SEQ ID NO 13  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 13

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu  
1                    5                    10                    15

Met Lys Glu Asp  
                  20

<210> SEQ ID NO 14  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 14

-continued

---

Lys Lys Trp Val Gln Asp Ser Met Lys Tyr Leu Asp Gln Lys Ser Pro  
 1 5 10 15

Thr Pro Lys Pro  
 20

<210> SEQ ID NO 15  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 15

Ser His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr  
 1 5 10 15

Asp Leu Pro Ala  
 20

<210> SEQ ID NO 16  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 16

Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala  
 1 5 10 15

Thr Glu Val Phe  
 20

<210> SEQ ID NO 17  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 17

Phe Pro Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu Val Phe Thr  
 1 5 10 15

Pro Val Val Pro  
 20

<210> SEQ ID NO 18  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 18

Phe Pro Thr Asp Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro  
 1 5 10 15

Thr Val Asp Thr  
 20

<210> SEQ ID NO 19  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 19

-continued

Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr  
 1 5 10 15

Asp Gly Arg Gly  
 20

<210> SEQ ID NO 20  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 20

Pro Gly Ala Gln Gly Leu Pro Gly Val Gly Leu Thr Pro Ser Ala Ala  
 1 5 10 15

Gln Thr Ala Arg  
 20

<210> SEQ ID NO 21  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 21

Arg Gly Glu Thr Arg Cys Glu Gln Asp Arg Pro Ser Pro Thr Thr Ala  
 1 5 10 15

Pro Pro Ala Pro  
 20

<210> SEQ ID NO 22  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 22

Glu Thr Arg Cys Glu Gln Asp Arg Pro Ser Pro Thr Thr Ala Pro Pro  
 1 5 10 15

Ala Pro Pro Ser  
 20

<210> SEQ ID NO 23  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 23

Thr Arg Cys Glu Gln Asp Arg Pro Ser Pro Thr Thr Ala Pro Pro Ala  
 1 5 10 15

Pro Pro Ser Pro  
 20

<210> SEQ ID NO 24  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

-continued

---

<400> SEQUENCE: 24

Pro Ser Pro Thr Thr Ala Pro Pro Ala Pro Pro Ser Pro Ser Pro Ser  
 1                   5                   10                   15

Pro Val Pro Lys  
                   20

<210> SEQ ID NO 25

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 25

Pro Thr Thr Ala Pro Pro Ala Pro Pro Ser Pro Ser Pro Ser Pro Val  
 1                   5                   10                   15

Pro Lys Ser Pro  
                   20

<210> SEQ ID NO 26

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 26

Thr Ala Pro Pro Ala Pro Pro Ser Pro Ser Pro Ser Pro Val Pro Lys  
 1                   5                   10                   15

Ser Pro Ser Val  
                   20

<210> SEQ ID NO 27

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 27

Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr Val Ala  
 1                   5                   10                   15

Pro Thr Ile His  
                   20

<210> SEQ ID NO 28

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 28

Asn Glu Phe Leu Cys Asp Lys Asp Lys Thr Ser Thr Val Ala Pro Thr  
 1                   5                   10                   15

Ile His Thr Thr  
                   20

<210> SEQ ID NO 29

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

-continued

&lt;400&gt; SEQUENCE: 29

Cys Asp Lys Asp Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr  
 1 5 10 15

Val Pro Ser Pro  
 20

&lt;210&gt; SEQ ID NO 30

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 30

Asp Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser  
 1 5 10 15

Pro Thr Thr Thr  
 20

&lt;210&gt; SEQ ID NO 31

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 31

Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro  
 1 5 10 15

Thr Thr Thr Pro  
 20

&lt;210&gt; SEQ ID NO 32

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 32

Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr  
 1 5 10 15

Pro Thr Pro Lys  
 20

&lt;210&gt; SEQ ID NO 33

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 33

Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr  
 1 5 10 15

Pro Lys Glu Lys  
 20

&lt;210&gt; SEQ ID NO 34

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

-continued

---

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 34

Pro Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr Pro  
 1 5 10 15

Lys Glu Lys Pro  
 20

<210> SEQ ID NO 35

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 35

Thr Ile His Thr Thr Val Pro Ser Pro Thr Thr Thr Pro Thr Pro Lys  
 1 5 10 15

Glu Lys Pro Glu  
 20

<210> SEQ ID NO 36

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 36

Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser Val Asn  
 1 5 10 15

Asn Gly Asn Asp  
 20

<210> SEQ ID NO 37

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 37

Ala Cys Leu Ala Val Ser Ala Gly Pro Val Pro Thr Pro Pro Asp Asn  
 1 5 10 15

Ile Gln Val Gln  
 20

<210> SEQ ID NO 38

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 38

Arg Arg Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln  
 1 5 10 15

Leu Val Thr Glu  
 20

<210> SEQ ID NO 39

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

-continued

---

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 39

Leu Asn Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro  
1 5 10 15

Ser Leu Phe Glu  
20

<210> SEQ ID NO 40

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 40

Asn Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro Ser  
1 5 10 15

Leu Phe Glu Phe  
20

<210> SEQ ID NO 41

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 41

Thr Phe Val Leu Ser Ala Leu Gln Pro Ser Pro Thr His Ser Ser Ser  
1 5 10 15

Asn Thr Gln Arg  
20

<210> SEQ ID NO 42

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 42

Arg Gln Gly Trp Ala Leu Arg Pro Val Leu Pro Thr Gln Ser Ala His  
1 5 10 15

Asp Pro Pro Ala  
20

<210> SEQ ID NO 43

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 43

Gln Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr  
1 5 10 15

Thr Asn Ala Ser  
20

<210> SEQ ID NO 44

<211> LENGTH: 20

<212> TYPE: PRT



-continued

---

<213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 44

Phe Leu Ser Leu Ser Gln Gly Gln Glu Ser Gln Thr Glu Leu Pro Asn  
 1                   5                   10                   15

Pro Arg Ile Ser  
 20

<210> SEQ ID NO 45  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 45

Leu Ser Leu Ala Leu Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr  
 1                   5                   10                   15

Lys Lys Thr Gln  
 20

<210> SEQ ID NO 46  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 46

Leu Ile Ser Pro Leu Ala Gln Ala Val Arg Ser Ser Ser Arg Thr Pro  
 1                   5                   10                   15

Ser Asp Lys Pro  
 20

<210> SEQ ID NO 47  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 47

Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser Phe Pro  
 1                   5                   10                   15

His Pro Gly Phe  
 20

<210> SEQ ID NO 48  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 48

Ser Glu Ser Phe Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn  
 1                   5                   10                   15

His Thr Arg Gln  
 20

<210> SEQ ID NO 49  
 <211> LENGTH: 20

-continued

---

<212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides  
  
 <400> SEQUENCE: 49  
  
 Ser Gly Trp Gly Ser Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp  
 1                   5                   10                   15  
  
 Leu Gln Cys Val  
                   20

<210> SEQ ID NO 50  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides  
  
 <400> SEQUENCE: 50  
  
 Arg Ile Gln Arg Gly Pro Gly Arg Ala Phe Val Thr Ile Gly Lys Ile  
 1                   5                   10                   15  
  
 Gly Asn Met Arg  
                   20

<210> SEQ ID NO 51  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides  
  
 <400> SEQUENCE: 51  
  
 Glu Met Ser Arg His Ser Leu Glu Gln Lys Pro Thr Asp Ala Pro Pro  
 1                   5                   10                   15  
  
 Lys Val Leu Thr  
                   20

<210> SEQ ID NO 52  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides  
  
 <400> SEQUENCE: 52  
  
 Cys Ser Glu Ser Leu Glu Leu Glu Asp Pro Ser Ser Gly Leu Gly Val  
 1                   5                   10                   15  
  
 Thr Lys Gln Asp  
                   20

<210> SEQ ID NO 53  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides  
  
 <400> SEQUENCE: 53  
  
 Leu Leu Glu Phe Tyr Leu Ala Met Pro Phe Ala Thr Pro Met Glu Ala  
 1                   5                   10                   15  
  
 Glu Leu Ala Arg  
                   20

<210> SEQ ID NO 54

-continued

<211> LENGTH: 203  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr  
 1 5 10 15  
 Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
 20 25 30  
 Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
 35 40 45  
 Thr Glu Lys Asn Ala Ile Pro Ala Pro Thr Thr Thr Lys Ser Cys Arg  
 50 55 60  
 Glu Thr Phe Leu Lys Cys Phe Cys Arg Phe Ile Asn Lys Gly Val Phe  
 65 70 75 80  
 Trp Ala Ser Pro Ile Leu Ser Ser Val Ser Asp Val Pro Phe Pro Phe  
 85 90 95  
 Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu  
 100 105 110  
 Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala  
 115 120 125  
 Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile  
 130 135 140  
 Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr  
 145 150 155 160  
 His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro  
 165 170 175  
 Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr  
 180 185 190  
 Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
 195 200

<210> SEQ ID NO 55  
 <211> LENGTH: 150  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr  
 1 5 10 15  
 Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
 20 25 30  
 Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
 35 40 45  
 Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp  
 50 55 60  
 Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Ala Val Cys Gln  
 65 70 75 80  
 Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp  
 85 90 95  
 Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg  
 100 105 110  
 Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser  
 115 120 125  
 Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala  
 130 135 140

-continued

Ala Thr Ser Ala Asn Leu  
145 150

<210> SEQ ID NO 56  
<211> LENGTH: 159  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr  
1 5 10 15  
Val Leu Thr Ala Thr Thr Ala Pro Lys Pro Ala Thr Val Val Thr Gly  
20 25 30  
Ser Gly His Ala Ser Ser Thr Pro Gly Gly Glu Lys Glu Thr Ser Ala  
35 40 45  
Thr Gln Arg Ser Ser Val Pro Ser Ser Thr Glu Lys Asn Ala Phe Asn  
50 55 60  
Ser Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg  
65 70 75 80  
Asp Ile Ser Glu Met Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly  
85 90 95  
Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu  
100 105 110  
Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr  
115 120 125  
Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser  
130 135 140  
Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu  
145 150 155

<210> SEQ ID NO 57  
<211> LENGTH: 14507  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Met Leu Lys Pro Ser Gly Leu Pro Gly Ser Ser Ser Pro Thr Arg Ser  
1 5 10 15  
Leu Met Thr Gly Ser Arg Ser Thr Lys Ala Thr Pro Glu Met Asp Ser  
20 25 30  
Gly Leu Thr Gly Ala Thr Leu Ser Pro Lys Thr Ser Thr Gly Ala Ile  
35 40 45  
Val Val Thr Glu His Thr Leu Pro Phe Thr Ser Pro Asp Lys Thr Leu  
50 55 60  
Ala Ser Pro Thr Ser Ser Val Val Gly Arg Thr Thr Gln Ser Leu Gly  
65 70 75 80  
Val Met Ser Ser Ala Leu Pro Glu Ser Thr Ser Arg Gly Met Thr His  
85 90 95  
Ser Glu Gln Arg Thr Ser Pro Ser Leu Ser Pro Gln Val Asn Gly Thr  
100 105 110  
Pro Ser Arg Asn Tyr Pro Ala Thr Ser Met Val Ser Gly Leu Ser Ser  
115 120 125  
Pro Arg Thr Arg Thr Ser Ser Thr Glu Gly Asn Phe Thr Lys Glu Ala  
130 135 140  
Ser Thr Tyr Thr Leu Thr Val Glu Thr Thr Ser Gly Pro Val Thr Glu  
145 150 155 160

-continued

---

Lys Tyr Thr Val Pro Thr Glu Thr Ser Thr Thr Glu Gly Asp Ser Thr  
 165 170 175  
 Glu Thr Pro Trp Asp Thr Arg Tyr Ile Pro Val Lys Ile Thr Ser Pro  
 180 185 190  
 Met Lys Thr Phe Ala Asp Ser Thr Ala Ser Lys Glu Asn Ala Pro Val  
 195 200 205  
 Ser Met Thr Pro Ala Glu Thr Thr Val Thr Asp Ser His Thr Pro Gly  
 210 215 220  
 Arg Thr Asn Pro Ser Phe Gly Thr Leu Tyr Ser Ser Phe Leu Asp Leu  
 225 230 235 240  
 Ser Pro Lys Gly Thr Pro Asn Ser Arg Gly Glu Thr Ser Leu Glu Leu  
 245 250 255  
 Ile Leu Ser Thr Thr Gly Tyr Pro Phe Ser Ser Pro Glu Pro Gly Ser  
 260 265 270  
 Ala Gly His Ser Arg Ile Ser Thr Ser Ala Pro Leu Ser Ser Ser Ala  
 275 280 285  
 Ser Val Leu Asp Asn Lys Ile Ser Glu Thr Ser Ile Phe Ser Gly Gln  
 290 295 300  
 Ser Leu Thr Ser Pro Leu Ser Pro Gly Val Pro Glu Ala Arg Ala Ser  
 305 310 315 320  
 Thr Met Pro Asn Ser Ala Ile Pro Phe Ser Met Thr Leu Ser Asn Ala  
 325 330 335  
 Glu Thr Ser Ala Glu Arg Val Arg Ser Thr Ile Ser Ser Leu Gly Thr  
 340 345 350  
 Pro Ser Ile Ser Thr Lys Gln Thr Ala Glu Thr Ile Leu Thr Phe His  
 355 360 365  
 Ala Phe Ala Glu Thr Met Asp Ile Pro Ser Thr His Ile Ala Lys Thr  
 370 375 380  
 Leu Ala Ser Glu Trp Leu Gly Ser Pro Gly Thr Leu Gly Gly Thr Ser  
 385 390 395 400  
 Thr Ser Ala Leu Thr Thr Thr Ser Pro Ser Thr Thr Leu Val Ser Glu  
 405 410 415  
 Glu Thr Asn Thr His His Ser Thr Ser Gly Lys Glu Thr Glu Gly Thr  
 420 425 430  
 Leu Asn Thr Ser Met Thr Pro Leu Glu Thr Ser Ala Pro Gly Glu Glu  
 435 440 445  
 Ser Glu Met Thr Ala Thr Leu Val Pro Thr Leu Gly Phe Thr Thr Leu  
 450 455 460  
 Asp Ser Lys Ile Arg Ser Pro Ser Gln Val Ser Ser Ser His Pro Thr  
 465 470 475 480  
 Arg Glu Leu Arg Thr Thr Gly Ser Thr Ser Gly Arg Gln Ser Ser Ser  
 485 490 495  
 Thr Ala Ala His Gly Ser Ser Asp Ile Leu Arg Ala Thr Thr Ser Ser  
 500 505 510  
 Thr Ser Lys Ala Ser Ser Trp Thr Ser Glu Ser Thr Ala Gln Gln Phe  
 515 520 525  
 Ser Glu Pro Gln His Thr Gln Trp Val Glu Thr Ser Pro Ser Met Lys  
 530 535 540  
 Thr Glu Arg Pro Pro Ala Ser Thr Ser Val Ala Ala Pro Ile Thr Thr  
 545 550 555 560  
 Ser Val Pro Ser Val Val Ser Gly Phe Thr Thr Leu Lys Thr Ser Ser  
 565 570 575

-continued

---

Thr Lys Gly Ile Trp Leu Glu Glu Thr Ser Ala Asp Thr Leu Ile Gly  
 580 585 590  
 Glu Ser Thr Ala Gly Pro Thr Thr His Gln Phe Ala Val Pro Thr Gly  
 595 600 605  
 Ile Ser Met Thr Gly Gly Ser Ser Thr Arg Gly Ser Gln Gly Thr Thr  
 610 615 620  
 His Leu Leu Thr Arg Ala Thr Ala Ser Ser Glu Thr Ser Ala Asp Leu  
 625 630 635 640  
 Thr Leu Ala Thr Asn Gly Val Pro Val Ser Val Ser Pro Ala Val Ser  
 645 650 655  
 Lys Thr Ala Ala Gly Ser Ser Pro Pro Gly Gly Thr Lys Pro Ser Tyr  
 660 665 670  
 Thr Met Val Ser Ser Val Ile Pro Glu Thr Ser Ser Leu Gln Ser Ser  
 675 680 685  
 Ala Phe Arg Glu Gly Thr Ser Leu Gly Leu Thr Pro Leu Asn Thr Arg  
 690 695 700  
 His Pro Phe Ser Ser Pro Glu Pro Asp Ser Ala Gly His Thr Lys Ile  
 705 710 715 720  
 Ser Thr Ser Ile Pro Leu Leu Ser Ser Ala Ser Val Leu Glu Asp Lys  
 725 730 735  
 Val Ser Ala Thr Ser Thr Phe Ser His His Lys Ala Thr Ser Ser Ile  
 740 745 750  
 Thr Thr Gly Thr Pro Glu Ile Ser Thr Lys Thr Lys Pro Ser Ser Ala  
 755 760 765  
 Val Leu Ser Ser Met Thr Leu Ser Asn Ala Ala Thr Ser Pro Glu Arg  
 770 775 780  
 Val Arg Asn Ala Thr Ser Pro Leu Thr His Pro Ser Pro Ser Gly Glu  
 785 790 795 800  
 Glu Thr Ala Gly Ser Val Leu Thr Leu Ser Thr Ser Ala Glu Thr Thr  
 805 810 815  
 Asp Ser Pro Asn Ile His Pro Thr Gly Thr Leu Thr Ser Glu Ser Ser  
 820 825 830  
 Glu Ser Pro Ser Thr Leu Ser Leu Pro Ser Val Ser Gly Val Lys Thr  
 835 840 845  
 Thr Phe Ser Ser Ser Thr Pro Ser Thr His Leu Phe Thr Ser Gly Glu  
 850 855 860  
 Glu Thr Glu Glu Thr Ser Asn Pro Ser Val Ser Gln Pro Glu Thr Ser  
 865 870 875 880  
 Val Ser Arg Val Arg Thr Thr Leu Ala Ser Thr Ser Val Pro Thr Pro  
 885 890 895  
 Val Phe Pro Thr Met Asp Thr Trp Pro Thr Arg Ser Ala Gln Phe Ser  
 900 905 910  
 Ser Ser His Leu Val Ser Glu Leu Arg Ala Thr Ser Ser Thr Ser Val  
 915 920 925  
 Thr Asn Ser Thr Gly Ser Ala Leu Pro Lys Ile Ser His Leu Thr Gly  
 930 935 940  
 Thr Ala Thr Met Ser Gln Thr Asn Arg Asp Thr Phe Asn Asp Ser Ala  
 945 950 955 960  
 Ala Pro Gln Ser Thr Thr Trp Pro Glu Thr Ser Pro Arg Phe Lys Thr  
 965 970 975  
 Gly Leu Pro Ser Ala Thr Thr Thr Val Ser Thr Ser Ala Thr Ser Leu  
 980 985 990  
 Ser Ala Thr Val Met Val Ser Lys Phe Thr Ser Pro Ala Thr Ser Ser

-continued

995				1000				1005						
Met	Glu	Ala	Thr	Ser	Ile	Arg	Glu	Pro	Ser	Thr	Thr	Ile	Leu	Thr
1010						1015						1020		
Thr	Glu	Thr	Thr	Asn	Gly	Pro	Gly	Ser	Met	Ala	Val	Ala	Ser	Thr
1025						1030						1035		
Asn	Ile	Pro	Ile	Gly	Lys	Gly	Tyr	Ile	Thr	Glu	Gly	Arg	Leu	Asp
1040						1045						1050		
Thr	Ser	His	Leu	Pro	Ile	Gly	Thr	Thr	Ala	Ser	Ser	Glu	Thr	Ser
1055						1060						1065		
Met	Asp	Phe	Thr	Met	Ala	Lys	Glu	Ser	Val	Ser	Met	Ser	Val	Ser
1070						1075						1080		
Pro	Ser	Gln	Ser	Met	Asp	Ala	Ala	Gly	Ser	Ser	Thr	Pro	Gly	Arg
1085						1090						1095		
Thr	Ser	Gln	Phe	Val	Asp	Thr	Phe	Ser	Asp	Asp	Val	Tyr	His	Leu
1100						1105						1110		
Thr	Ser	Arg	Glu	Ile	Thr	Ile	Pro	Arg	Asp	Gly	Thr	Ser	Ser	Ala
1115						1120						1125		
Leu	Thr	Pro	Gln	Met	Thr	Ala	Thr	His	Pro	Pro	Ser	Pro	Asp	Pro
1130						1135						1140		
Gly	Ser	Ala	Arg	Ser	Thr	Trp	Leu	Gly	Ile	Leu	Ser	Ser	Ser	Pro
1145						1150						1155		
Ser	Ser	Pro	Thr	Pro	Lys	Val	Thr	Met	Ser	Ser	Thr	Phe	Ser	Thr
1160						1165						1170		
Gln	Arg	Val	Thr	Thr	Ser	Met	Ile	Met	Asp	Thr	Val	Glu	Thr	Ser
1175						1180						1185		
Arg	Trp	Asn	Met	Pro	Asn	Leu	Pro	Ser	Thr	Thr	Ser	Leu	Thr	Pro
1190						1195						1200		
Ser	Asn	Ile	Pro	Thr	Ser	Gly	Ala	Ile	Gly	Lys	Ser	Thr	Leu	Val
1205						1210						1215		
Pro	Leu	Asp	Thr	Pro	Ser	Pro	Ala	Thr	Ser	Leu	Glu	Ala	Ser	Glu
1220						1225						1230		
Gly	Gly	Leu	Pro	Thr	Leu	Ser	Thr	Tyr	Pro	Glu	Ser	Thr	Asn	Thr
1235						1240						1245		
Pro	Ser	Ile	His	Leu	Gly	Ala	His	Ala	Ser	Ser	Glu	Ser	Pro	Ser
1250						1255						1260		
Thr	Ile	Lys	Leu	Thr	Met	Ala	Ser	Val	Val	Lys	Pro	Gly	Ser	Tyr
1265						1270						1275		
Thr	Pro	Leu	Thr	Phe	Pro	Ser	Ile	Glu	Thr	His	Ile	His	Val	Ser
1280						1285						1290		
Thr	Ala	Arg	Met	Ala	Tyr	Ser	Ser	Gly	Ser	Ser	Pro	Glu	Met	Thr
1295						1300						1305		
Ala	Pro	Gly	Glu	Thr	Asn	Thr	Gly	Ser	Thr	Trp	Asp	Pro	Thr	Thr
1310						1315						1320		
Tyr	Ile	Thr	Thr	Thr	Asp	Pro	Lys	Asp	Thr	Ser	Ser	Ala	Gln	Val
1325						1330						1335		
Ser	Thr	Pro	His	Ser	Val	Arg	Thr	Leu	Arg	Thr	Thr	Glu	Asn	His
1340						1345						1350		
Pro	Lys	Thr	Glu	Ser	Ala	Thr	Pro	Ala	Ala	Tyr	Ser	Gly	Ser	Pro
1355						1360						1365		
Lys	Ile	Ser	Ser	Ser	Pro	Asn	Leu	Thr	Ser	Pro	Ala	Thr	Lys	Ala
1370						1375						1380		
Trp	Thr	Ile	Thr	Asp	Thr	Thr	Glu	His	Ser	Thr	Gln	Leu	His	Tyr
1385						1390						1395		

-continued

---

Thr Lys	Leu Ala	Glu Lys	Ser Ser	Gly Phe	Glu Thr	Gln Ser	Ala		
1400			1405		1410				
Pro Gly	Pro Val	Ser Val	Val Val	Ile Pro	Thr Ser	Pro Thr	Ile Gly		
1415			1420			1425			
Ser Ser	Thr Leu	Glu Leu	Thr Thr	Ser Asp	Val Pro	Gly Glu	Pro Leu		
1430			1435			1440			
Val Leu	Ala Pro	Ser Glu	Gln Thr	Thr Thr	Ile Thr	Leu Pro	Met Ala		
1445			1450			1455			
Thr Trp	Leu Ser	Thr Ser	Leu Thr	Glu Glu	Met Ala	Ser Thr	Asp		
1460			1465			1470			
Leu Asp	Ile Ser	Ser Pro	Ser Ser	Pro Met	Ser Thr	Phe Ala	Ile		
1475			1480			1485			
Phe Pro	Pro Met	Ser Thr	Pro Ser	Ser His	Glu Leu	Ser Lys	Ser Glu		
1490			1495			1500			
Ala Asp	Thr Ser	Ala Ile	Arg Asn	Thr Asp	Ser Thr	Thr Leu	Asp		
1505			1510			1515			
Gln His	Leu Gly	Ile Arg	Ser Leu	Gly Arg	Thr Gly	Asp Leu	Thr		
1520			1525			1530			
Thr Val	Pro Ile	Thr Pro	Leu Thr	Thr Thr	Trp Thr	Ser Val	Ile		
1535			1540			1545			
Glu His	Ser Thr	Gln Ala	Gln Asp	Thr Leu	Ser Ala	Thr Met	Ser		
1550			1555			1560			
Pro Thr	His Val	Thr Gln	Ser Leu	Lys Asp	Gln Thr	Ser Ile	Pro		
1565			1570			1575			
Ala Ser	Ala Ser	Pro Ser	His Leu	Thr Glu	Val Tyr	Pro Glu	Leu		
1580			1585			1590			
Gly Thr	Gln Gly	Arg Ser	Ser Ser	Ser Glu	Ala Thr	Thr Phe	Trp Lys		
1595			1600			1605			
Pro Ser	Thr Asp	Thr Leu	Ser Arg	Glu Ile	Glu Thr	Gly Pro	Thr		
1610			1615			1620			
Asn Ile	Gln Ser	Thr Pro	Pro Met	Asp Asn	Thr Thr	Thr Gly	Ser		
1625			1630			1635			
Ser Ser	Ser Gly	Val Thr	Leu Gly	Ile Ala	His Leu	Pro Ile	Gly		
1640			1645			1650			
Thr Ser	Ser Pro	Ala Glu	Thr Ser	Thr Asn	Met Ala	Leu Glu	Arg		
1655			1660			1665			
Arg Ser	Ser Thr	Ala Thr	Val Ser	Met Ala	Gly Thr	Met Gly	Leu		
1670			1675			1680			
Leu Val	Thr Ser	Ala Pro	Gly Arg	Ser Ile	Ser Gln	Ser Leu	Gly		
1685			1690			1695			
Arg Val	Ser Ser	Val Leu	Ser Glu	Ser Thr	Thr Thr	Gly Val	Thr		
1700			1705			1710			
Asp Ser	Ser Lys	Gly Ser	Ser Pro	Arg Leu	Asn Thr	Gln Gly	Asn		
1715			1720			1725			
Thr Ala	Leu Ser	Ser Ser	Leu Glu	Pro Ser	Tyr Ala	Glu Gly	Ser		
1730			1735			1740			
Gln Met	Ser Thr	Ser Ile	Pro Leu	Thr Ser	Ser Pro	Thr Thr	Pro		
1745			1750			1755			
Asp Val	Glu Phe	Ile Gly	Gly Ser	Thr Phe	Trp Thr	Lys Glu	Val		
1760			1765			1770			
Thr Thr	Val Met	Thr Ser	Asp Ile	Ser Lys	Ser Ser	Ala Arg	Thr		
1775			1780			1785			



-continued

Glu	Ser	Ser	Ser	Ala	Thr	Leu	Met	Ser	Thr	Ala	Leu	Gly	Ser	Thr	1790	1795	1800
Glu	Asn	Thr	Gly	Lys	Glu	Lys	Leu	Arg	Thr	Ala	Ser	Met	Asp	Leu	1805	1810	1815
Pro	Ser	Pro	Thr	Pro	Ser	Met	Glu	Val	Thr	Pro	Trp	Ile	Ser	Leu	1820	1825	1830
Thr	Leu	Ser	Asn	Ala	Pro	Asn	Thr	Thr	Asp	Ser	Leu	Asp	Leu	Ser	1835	1840	1845
His	Gly	Val	His	Thr	Ser	Ser	Ala	Gly	Thr	Leu	Ala	Thr	Asp	Arg	1850	1855	1860
Ser	Leu	Asn	Thr	Gly	Val	Thr	Arg	Ala	Ser	Arg	Leu	Glu	Asn	Gly	1865	1870	1875
Ser	Asp	Thr	Ser	Ser	Lys	Ser	Leu	Ser	Met	Gly	Asn	Ser	Thr	His	1880	1885	1890
Thr	Ser	Met	Thr	Tyr	Thr	Glu	Lys	Ser	Glu	Val	Ser	Ser	Ser	Ile	1895	1900	1905
His	Pro	Arg	Pro	Glu	Thr	Ser	Ala	Pro	Gly	Ala	Glu	Thr	Thr	Leu	1910	1915	1920
Thr	Ser	Thr	Pro	Gly	Asn	Arg	Ala	Ile	Ser	Leu	Thr	Leu	Pro	Phe	1925	1930	1935
Ser	Ser	Ile	Pro	Val	Glu	Glu	Val	Ile	Ser	Thr	Gly	Ile	Thr	Ser	1940	1945	1950
Gly	Pro	Asp	Ile	Asn	Ser	Ala	Pro	Met	Thr	His	Ser	Pro	Ile	Thr	1955	1960	1965
Pro	Pro	Thr	Ile	Val	Trp	Thr	Ser	Thr	Gly	Thr	Ile	Glu	Gln	Ser	1970	1975	1980
Thr	Gln	Pro	Leu	His	Ala	Val	Ser	Ser	Glu	Lys	Val	Ser	Val	Gln	1985	1990	1995
Thr	Gln	Ser	Thr	Pro	Tyr	Val	Asn	Ser	Val	Ala	Val	Ser	Ala	Ser	2000	2005	2010
Pro	Thr	His	Glu	Asn	Ser	Val	Ser	Ser	Gly	Ser	Ser	Thr	Ser	Ser	2015	2020	2025
Pro	Tyr	Ser	Ser	Ala	Ser	Leu	Glu	Ser	Leu	Asp	Ser	Thr	Ile	Ser	2030	2035	2040
Arg	Arg	Asn	Ala	Ile	Thr	Ser	Trp	Leu	Trp	Asp	Leu	Thr	Thr	Ser	2045	2050	2055
Leu	Pro	Thr	Thr	Thr	Trp	Pro	Ser	Thr	Ser	Leu	Ser	Glu	Ala	Leu	2060	2065	2070
Ser	Ser	Gly	His	Ser	Gly	Val	Ser	Asn	Pro	Ser	Ser	Thr	Thr	Thr	2075	2080	2085
Glu	Phe	Pro	Leu	Phe	Ser	Ala	Ala	Ser	Thr	Ser	Ala	Ala	Lys	Gln	2090	2095	2100
Arg	Asn	Pro	Glu	Thr	Glu	Thr	His	Gly	Pro	Gln	Asn	Thr	Ala	Ala	2105	2110	2115
Ser	Thr	Leu	Asn	Thr	Asp	Ala	Ser	Ser	Val	Thr	Gly	Leu	Ser	Glu	2120	2125	2130
Thr	Pro	Val	Gly	Ala	Ser	Ile	Ser	Ser	Glu	Val	Pro	Leu	Pro	Met	2135	2140	2145
Ala	Ile	Thr	Ser	Arg	Ser	Asp	Val	Ser	Gly	Leu	Thr	Ser	Glu	Ser	2150	2155	2160
Thr	Ala	Asn	Pro	Ser	Leu	Gly	Thr	Ala	Ser	Ser	Ala	Gly	Thr	Lys	2165	2170	2175
Leu	Thr	Arg	Thr	Ile	Ser	Leu	Pro	Thr	Ser	Glu	Ser	Leu	Val	Ser			

-continued

---

2180		2185		2190
Phe Arg Met Asn Lys Asp Pro Trp Thr Val Ser Ile Pro Leu Gly				
2195		2200		2205
Ser His Pro Thr Thr Asn Thr Glu Thr Ser Ile Pro Val Asn Ser				
2210		2215		2220
Ala Gly Pro Pro Gly Leu Ser Thr Val Ala Ser Asp Val Ile Asp				
2225		2230		2235
Thr Pro Ser Asp Gly Ala Glu Ser Ile Pro Thr Val Ser Phe Ser				
2240		2245		2250
Pro Ser Pro Asp Thr Glu Val Thr Thr Ile Ser His Phe Pro Glu				
2255		2260		2265
Lys Thr Thr His Ser Phe Arg Thr Ile Ser Ser Leu Thr His Glu				
2270		2275		2280
Leu Thr Ser Arg Val Thr Pro Ile Pro Gly Asp Trp Met Ser Ser				
2285		2290		2295
Ala Met Ser Thr Lys Pro Thr Gly Ala Ser Pro Ser Ile Thr Leu				
2300		2305		2310
Gly Glu Arg Arg Thr Ile Thr Ser Ala Ala Pro Thr Thr Ser Pro				
2315		2320		2325
Ile Val Leu Thr Ala Ser Phe Thr Glu Thr Ser Thr Val Ser Leu				
2330		2335		2340
Asp Asn Glu Thr Thr Val Lys Thr Ser Asp Ile Leu Asp Ala Arg				
2345		2350		2355
Lys Thr Asn Glu Leu Pro Ser Asp Ser Ser Ser Ser Ser Asp Leu				
2360		2365		2370
Ile Asn Thr Ser Ile Ala Ser Ser Thr Met Asp Val Thr Lys Thr				
2375		2380		2385
Ala Ser Ile Ser Pro Thr Ser Ile Ser Gly Met Thr Ala Ser Ser				
2390		2395		2400
Ser Pro Ser Leu Phe Ser Ser Asp Arg Pro Gln Val Pro Thr Ser				
2405		2410		2415
Thr Thr Glu Thr Asn Thr Ala Thr Ser Pro Ser Val Ser Ser Asn				
2420		2425		2430
Thr Tyr Ser Leu Asp Gly Gly Ser Asn Val Gly Gly Thr Pro Ser				
2435		2440		2445
Thr Leu Pro Pro Phe Thr Ile Thr His Pro Val Glu Thr Ser Ser				
2450		2455		2460
Ala Leu Leu Ala Trp Ser Arg Pro Val Arg Thr Phe Ser Thr Met				
2465		2470		2475
Val Ser Thr Asp Thr Ala Ser Gly Glu Asn Pro Thr Ser Ser Asn				
2480		2485		2490
Ser Val Val Thr Ser Val Pro Ala Pro Gly Thr Trp Thr Ser Val				
2495		2500		2505
Gly Ser Thr Thr Asp Leu Pro Ala Met Gly Phe Leu Lys Thr Ser				
2510		2515		2520
Pro Ala Gly Glu Ala His Ser Leu Leu Ala Ser Thr Ile Glu Pro				
2525		2530		2535
Ala Thr Ala Phe Thr Pro His Leu Ser Ala Ala Val Val Thr Gly				
2540		2545		2550
Ser Ser Ala Thr Ser Glu Ala Ser Leu Leu Thr Thr Ser Glu Ser				
2555		2560		2565
Lys Ala Ile His Ser Ser Pro Gln Thr Pro Thr Thr Pro Thr Ser				
2570		2575		2580

-continued

---

Gly	Ala	Asn	Trp	Glu	Thr	Ser	Ala	Thr	Pro	Glu	Ser	Leu	Leu	Val
2585						2590					2595			
Val	Thr	Glu	Thr	Ser	Asp	Thr	Thr	Leu	Thr	Ser	Lys	Ile	Leu	Val
2600						2605					2610			
Thr	Asp	Thr	Ile	Leu	Phe	Ser	Thr	Val	Ser	Thr	Pro	Pro	Ser	Lys
2615						2620					2625			
Phe	Pro	Ser	Thr	Gly	Thr	Leu	Ser	Gly	Ala	Ser	Phe	Pro	Thr	Leu
2630						2635					2640			
Leu	Pro	Asp	Thr	Pro	Ala	Ile	Pro	Leu	Thr	Ala	Thr	Glu	Pro	Thr
2645						2650					2655			
Ser	Ser	Leu	Ala	Thr	Ser	Phe	Asp	Ser	Thr	Pro	Leu	Val	Thr	Ile
2660						2665					2670			
Ala	Ser	Asp	Ser	Leu	Gly	Thr	Val	Pro	Glu	Thr	Thr	Leu	Thr	Met
2675						2680					2685			
Ser	Glu	Thr	Ser	Asn	Gly	Asp	Ala	Leu	Val	Leu	Lys	Thr	Val	Ser
2690						2695					2700			
Asn	Pro	Asp	Arg	Ser	Ile	Pro	Gly	Ile	Thr	Ile	Gln	Gly	Val	Thr
2705						2710					2715			
Glu	Ser	Pro	Leu	His	Pro	Ser	Ser	Thr	Ser	Pro	Ser	Lys	Ile	Val
2720						2725					2730			
Ala	Pro	Arg	Asn	Thr	Thr	Tyr	Glu	Gly	Ser	Ile	Thr	Val	Ala	Leu
2735						2740					2745			
Ser	Thr	Leu	Pro	Ala	Gly	Thr	Thr	Gly	Ser	Leu	Val	Phe	Ser	Gln
2750						2755					2760			
Ser	Ser	Glu	Asn	Ser	Glu	Thr	Thr	Ala	Leu	Val	Asp	Ser	Ser	Ala
2765						2770					2775			
Gly	Leu	Glu	Arg	Ala	Ser	Val	Met	Pro	Leu	Thr	Thr	Gly	Ser	Gln
2780						2785					2790			
Gly	Met	Ala	Ser	Ser	Gly	Gly	Ile	Arg	Ser	Gly	Ser	Thr	His	Ser
2795						2800					2805			
Thr	Gly	Thr	Lys	Thr	Phe	Ser	Ser	Leu	Pro	Leu	Thr	Met	Asn	Pro
2810						2815					2820			
Gly	Glu	Val	Thr	Ala	Met	Ser	Glu	Ile	Thr	Thr	Asn	Arg	Leu	Thr
2825						2830					2835			
Ala	Thr	Gln	Ser	Thr	Ala	Pro	Lys	Gly	Ile	Pro	Val	Lys	Pro	Thr
2840						2845					2850			
Ser	Ala	Glu	Ser	Gly	Leu	Leu	Thr	Pro	Val	Ser	Ala	Ser	Ser	Ser
2855						2860					2865			
Pro	Ser	Lys	Ala	Phe	Ala	Ser	Leu	Thr	Thr	Ala	Pro	Pro	Thr	Trp
2870						2875					2880			
Gly	Ile	Pro	Gln	Ser	Thr	Leu	Thr	Phe	Glu	Phe	Ser	Glu	Val	Pro
2885						2890					2895			
Ser	Leu	Asp	Thr	Lys	Ser	Ala	Ser	Leu	Pro	Thr	Pro	Gly	Gln	Ser
2900						2905					2910			
Leu	Asn	Thr	Ile	Pro	Asp	Ser	Asp	Ala	Ser	Thr	Ala	Ser	Ser	Ser
2915						2920					2925			
Leu	Ser	Lys	Ser	Pro	Glu	Lys	Asn	Pro	Arg	Ala	Arg	Met	Met	Thr
2930						2935					2940			
Ser	Thr	Lys	Ala	Ile	Ser	Ala	Ser	Ser	Phe	Gln	Ser	Thr	Gly	Phe
2945						2950					2955			
Thr	Glu	Thr	Pro	Glu	Gly	Ser	Ala	Ser	Pro	Ser	Met	Ala	Gly	His
2960						2965					2970			

-continued

Glu	Pro	Arg	Val	Pro	Thr	Ser	Gly	Thr	Gly	Asp	Pro	Arg	Tyr	Ala
2975						2980					2985			
Ser	Glu	Ser	Met	Ser	Tyr	Pro	Asp	Pro	Ser	Lys	Ala	Ser	Ser	Ala
2990						2995					3000			
Met	Thr	Ser	Thr	Ser	Leu	Ala	Ser	Lys	Leu	Thr	Thr	Leu	Phe	Ser
3005						3010					3015			
Thr	Gly	Gln	Ala	Ala	Arg	Ser	Gly	Ser	Ser	Ser	Ser	Pro	Ile	Ser
3020						3025					3030			
Leu	Ser	Thr	Glu	Lys	Glu	Thr	Ser	Phe	Leu	Ser	Pro	Thr	Ala	Ser
3035						3040					3045			
Thr	Ser	Arg	Lys	Thr	Ser	Leu	Phe	Leu	Gly	Pro	Ser	Met	Ala	Arg
3050						3055					3060			
Gln	Pro	Asn	Ile	Leu	Val	His	Leu	Gln	Thr	Ser	Ala	Leu	Thr	Leu
3065						3070					3075			
Ser	Pro	Thr	Ser	Thr	Leu	Asn	Met	Ser	Gln	Glu	Glu	Pro	Pro	Glu
3080						3085					3090			
Leu	Thr	Ser	Ser	Gln	Thr	Ile	Ala	Glu	Glu	Glu	Gly	Thr	Thr	Ala
3095						3100					3105			
Glu	Thr	Gln	Thr	Leu	Thr	Phe	Thr	Pro	Ser	Glu	Thr	Pro	Thr	Ser
3110						3115					3120			
Leu	Leu	Pro	Val	Ser	Ser	Pro	Thr	Glu	Pro	Thr	Ala	Arg	Arg	Lys
3125						3130					3135			
Ser	Ser	Pro	Glu	Thr	Trp	Ala	Ser	Ser	Ile	Ser	Val	Pro	Ala	Lys
3140						3145					3150			
Thr	Ser	Leu	Val	Glu	Thr	Thr	Asp	Gly	Thr	Leu	Val	Thr	Thr	Ile
3155						3160					3165			
Lys	Met	Ser	Ser	Gln	Ala	Ala	Gln	Gly	Asn	Ser	Thr	Trp	Pro	Ala
3170						3175					3180			
Pro	Ala	Glu	Glu	Thr	Gly	Ser	Ser	Pro	Ala	Gly	Thr	Ser	Pro	Gly
3185						3190					3195			
Ser	Pro	Glu	Met	Ser	Thr	Thr	Leu	Lys	Ile	Met	Ser	Ser	Lys	Glu
3200						3205					3210			
Pro	Ser	Ile	Ser	Pro	Glu	Ile	Arg	Ser	Thr	Val	Arg	Asn	Ser	Pro
3215						3220					3225			
Trp	Lys	Thr	Pro	Glu	Thr	Thr	Val	Pro	Met	Glu	Thr	Thr	Val	Glu
3230						3235					3240			
Pro	Val	Thr	Leu	Gln	Ser	Thr	Ala	Leu	Gly	Ser	Gly	Ser	Thr	Ser
3245						3250					3255			
Ile	Ser	His	Leu	Pro	Thr	Gly	Thr	Thr	Ser	Pro	Thr	Lys	Ser	Pro
3260						3265					3270			
Thr	Glu	Asn	Met	Leu	Ala	Thr	Glu	Arg	Val	Ser	Leu	Ser	Pro	Ser
3275						3280					3285			
Pro	Pro	Glu	Ala	Trp	Thr	Asn	Leu	Tyr	Ser	Gly	Thr	Pro	Gly	Gly
3290						3295					3300			
Thr	Arg	Gln	Ser	Leu	Ala	Thr	Met	Ser	Ser	Val	Ser	Leu	Glu	Ser
3305						3310					3315			
Pro	Thr	Ala	Arg	Ser	Ile	Thr	Gly	Thr	Gly	Gln	Gln	Ser	Ser	Pro
3320						3325					3330			
Glu	Leu	Val	Ser	Lys	Thr	Thr	Gly	Met	Glu	Phe	Ser	Met	Trp	His
3335						3340					3345			
Gly	Ser	Thr	Gly	Gly	Thr	Thr	Gly	Asp	Thr	His	Val	Ser	Leu	Ser
3350						3355					3360			
Thr	Ser	Ser	Asn	Ile	Leu	Glu	Asp	Pro	Val	Thr	Ser	Pro	Asn	Ser



-continued

---

Ile Ser	Pro Ala	Thr Ser	Gln Leu	Pro Phe	Ser Ile	Gly His	Ile Ile	3770	3775	3780
Thr Ser	Ala Val	Thr Pro	Ala Ala	Met Ala	Arg Ser	Ser Gly	Val Val	3785	3790	3795
Thr Phe	Ser Arg	Pro Asp	Pro Thr	Ser Lys	Lys Ala	Glu Gln	Thr Thr	3800	3805	3810
Ser Thr	Gln Leu	Pro Thr	Thr Thr	Ser Ala	His Pro	Gly Gln	Val Val	3815	3820	3825
Pro Arg	Ser Ala	Ala Thr	Thr Thr	Leu Asp	Val Ile	Pro His	Thr Ala	3830	3835	3840
Lys Thr	Pro Asp	Ala Thr	Phe Gln	Arg Gln	Gly Gln	Thr Ala	Leu Leu	3845	3850	3855
Thr Thr	Glu Ala	Arg Ala	Thr Ser	Asp Ser	Trp Asn	Glu Lys	Glu Glu	3860	3865	3870
Lys Ser	Thr Pro	Ser Ala	Pro Trp	Ile Thr	Glu Met	Met Asn	Ser Ser	3875	3880	3885
Val Ser	Glu Asp	Thr Ile	Lys Glu	Val Thr	Ser Ser	Ser Ser	Val Val	3890	3895	3900
Leu Arg	Thr Leu	Asn Thr	Leu Asp	Ile Asn	Leu Glu	Ser Gly	Thr Thr	3905	3910	3915
Thr Ser	Ser Pro	Ser Trp	Lys Ser	Ser Pro	Tyr Glu	Arg Ile	Ala Ala	3920	3925	3930
Pro Ser	Glu Ser	Thr Thr	Asp Lys	Glu Ala	Ile His	Pro Ser	Thr Thr	3935	3940	3945
Asn Thr	Val Glu	Thr Thr	Gly Trp	Val Thr	Ser Ser	Glu His	Ala Ala	3950	3955	3960
Ser His	Ser Thr	Ile Pro	Ala His	Ser Ala	Ser Ser	Lys Leu	Thr Thr	3965	3970	3975
Ser Pro	Val Val	Thr Thr	Ser Thr	Arg Glu	Gln Ala	Ile Val	Ser Ser	3980	3985	3990
Met Ser	Thr Thr	Thr Trp	Pro Glu	Ser Thr	Arg Ala	Arg Thr	Glu Glu	3995	4000	4005
Pro Asn	Ser Phe	Leu Thr	Ile Glu	Leu Arg	Asp Val	Ser Pro	Tyr Tyr	4010	4015	4020
Met Asp	Thr Ser	Ser Thr	Thr Gln	Thr Ser	Ile Ile	Ser Ser	Pro Pro	4025	4030	4035
Gly Ser	Thr Ala	Ile Thr	Lys Gly	Pro Arg	Thr Glu	Ile Thr	Ser Ser	4040	4045	4050
Ser Lys	Arg Ile	Ser Ser	Ser Phe	Leu Ala	Gln Ser	Met Arg	Ser Ser	4055	4060	4065
Ser Asp	Ser Pro	Ser Glu	Ala Ile	Thr Arg	Leu Ser	Asn Phe	Pro Pro	4070	4075	4080
Ala Met	Thr Glu	Ser Gly	Gly Met	Ile Leu	Ala Met	Gln Thr	Ser Ser	4085	4090	4095
Pro Pro	Gly Ala	Thr Ser	Leu Ser	Ala Pro	Thr Leu	Asp Thr	Ser Ser	4100	4105	4110
Ala Thr	Ala Ser	Trp Thr	Gly Thr	Pro Leu	Ala Thr	Thr Gln	Arg Arg	4115	4120	4125
Phe Thr	Tyr Ser	Glu Lys	Thr Thr	Leu Phe	Ser Lys	Gly Pro	Glu Glu	4130	4135	4140
Asp Thr	Ser Gln	Pro Ser	Pro Pro	Ser Val	Glu Glu	Thr Ser	Ser Ser	4145	4150	4155

-continued

Ser	Ser	Ser	Leu	Val	Pro	Ile	His	Ala	Thr	Thr	Ser	Pro	Ser	Asn
4160						4165					4170			
Ile	Leu	Leu	Thr	Ser	Gln	Gly	His	Ser	Pro	Ser	Ser	Thr	Pro	Pro
4175						4180					4185			
Val	Thr	Ser	Val	Phe	Leu	Ser	Glu	Thr	Ser	Gly	Leu	Gly	Lys	Thr
4190						4195					4200			
Thr	Asp	Met	Ser	Arg	Ile	Ser	Leu	Glu	Pro	Gly	Thr	Ser	Leu	Pro
4205						4210					4215			
Pro	Asn	Leu	Ser	Ser	Thr	Ala	Gly	Glu	Ala	Leu	Ser	Thr	Tyr	Glu
4220						4225					4230			
Ala	Ser	Arg	Asp	Thr	Lys	Ala	Ile	His	His	Ser	Ala	Asp	Thr	Ala
4235						4240					4245			
Val	Thr	Asn	Met	Glu	Ala	Thr	Ser	Ser	Glu	Tyr	Ser	Pro	Ile	Pro
4250						4255					4260			
Gly	His	Thr	Lys	Pro	Ser	Lys	Ala	Thr	Ser	Pro	Leu	Val	Thr	Ser
4265						4270					4275			
His	Ile	Met	Gly	Asp	Ile	Thr	Ser	Ser	Thr	Ser	Val	Phe	Gly	Ser
4280						4285					4290			
Ser	Glu	Thr	Thr	Glu	Ile	Glu	Thr	Val	Ser	Ser	Val	Asn	Gln	Gly
4295						4300					4305			
Leu	Gln	Glu	Arg	Ser	Thr	Ser	Gln	Val	Ala	Ser	Ser	Ala	Thr	Glu
4310						4315					4320			
Thr	Ser	Thr	Val	Ile	Thr	His	Val	Ser	Ser	Gly	Asp	Ala	Thr	Thr
4325						4330					4335			
His	Val	Thr	Lys	Thr	Gln	Ala	Thr	Phe	Ser	Ser	Gly	Thr	Ser	Ile
4340						4345					4350			
Ser	Ser	Pro	His	Gln	Phe	Ile	Thr	Ser	Thr	Asn	Thr	Phe	Thr	Asp
4355						4360					4365			
Val	Ser	Thr	Asn	Pro	Ser	Thr	Ser	Leu	Ile	Met	Thr	Glu	Ser	Ser
4370						4375					4380			
Gly	Val	Thr	Ile	Thr	Thr	Gln	Thr	Gly	Pro	Thr	Gly	Ala	Ala	Thr
4385						4390					4395			
Gln	Gly	Pro	Tyr	Leu	Leu	Asp	Thr	Ser	Thr	Met	Pro	Tyr	Leu	Thr
4400						4405					4410			
Glu	Thr	Pro	Leu	Ala	Val	Thr	Pro	Asp	Phe	Met	Gln	Ser	Glu	Lys
4415						4420					4425			
Thr	Thr	Leu	Ile	Ser	Lys	Gly	Pro	Lys	Asp	Val	Ser	Trp	Thr	Ser
4430						4435					4440			
Pro	Pro	Ser	Val	Ala	Glu	Thr	Ser	Tyr	Pro	Ser	Ser	Leu	Thr	Pro
4445						4450					4455			
Phe	Leu	Val	Thr	Thr	Ile	Pro	Pro	Ala	Thr	Ser	Thr	Leu	Gln	Gly
4460						4465					4470			
Gln	His	Thr	Ser	Ser	Pro	Val	Ser	Ala	Thr	Ser	Val	Leu	Thr	Ser
4475						4480					4485			
Gly	Leu	Val	Lys	Thr	Thr	Asp	Met	Leu	Asn	Thr	Ser	Met	Glu	Pro
4490						4495					4500			
Val	Thr	Asn	Ser	Pro	Gln	Asn	Leu	Asn	Asn	Pro	Ser	Asn	Glu	Ile
4505						4510					4515			
Leu	Ala	Thr	Leu	Ala	Ala	Thr	Thr	Asp	Ile	Glu	Thr	Ile	His	Pro
4520						4525					4530			
Ser	Ile	Asn	Lys	Ala	Val	Thr	Asn	Met	Gly	Thr	Ala	Ser	Ser	Ala
4535						4540					4545			
His	Val	Leu	His	Ser	Thr	Leu	Pro	Val	Ser	Ser	Glu	Pro	Ser	Thr

-continued

---

4550	4555	4560
Ala Thr Ser Pro Met Val Pro Ala Ser Ser Met Gly Asp Ala Leu 4565 4570 4575		
Ala Ser Ile Ser Ile Pro Gly Ser Glu Thr Thr Asp Ile Glu Gly 4580 4585 4590		
Glu Pro Thr Ser Ser Leu Thr Ala Gly Arg Lys Glu Asn Ser Thr 4595 4600 4605		
Leu Gln Glu Met Asn Ser Thr Thr Glu Ser Asn Ile Ile Leu Ser 4610 4615 4620		
Asn Val Ser Val Gly Ala Ile Thr Glu Ala Thr Lys Met Glu Val 4625 4630 4635		
Pro Ser Phe Asp Ala Thr Phe Ile Pro Thr Pro Ala Gln Ser Thr 4640 4645 4650		
Lys Phe Pro Asp Ile Phe Ser Val Ala Ser Ser Arg Leu Ser Asn 4655 4660 4665		
Ser Pro Pro Met Thr Ile Ser Thr His Met Thr Thr Thr Gln Thr 4670 4675 4680		
Gly Ser Ser Gly Ala Thr Ser Lys Ile Pro Leu Ala Leu Asp Thr 4685 4690 4695		
Ser Thr Leu Glu Thr Ser Ala Gly Thr Pro Ser Val Val Thr Glu 4700 4705 4710		
Gly Phe Ala His Ser Lys Ile Thr Thr Ala Met Asn Asn Asp Val 4715 4720 4725		
Lys Asp Val Ser Gln Thr Asn Pro Pro Phe Gln Asp Glu Ala Ser 4730 4735 4740		
Ser Pro Ser Ser Gln Ala Pro Val Leu Val Thr Thr Leu Pro Ser 4745 4750 4755		
Ser Val Ala Phe Thr Pro Gln Trp His Ser Thr Ser Ser Pro Val 4760 4765 4770		
Ser Met Ser Ser Val Leu Thr Ser Ser Leu Val Lys Thr Ala Gly 4775 4780 4785		
Lys Val Asp Thr Ser Leu Glu Thr Val Thr Ser Ser Pro Gln Ser 4790 4795 4800		
Met Ser Asn Thr Leu Asp Asp Ile Ser Val Thr Ser Ala Ala Thr 4805 4810 4815		
Thr Asp Ile Glu Thr Thr His Pro Ser Ile Asn Thr Val Val Thr 4820 4825 4830		
Asn Val Gly Thr Thr Gly Ser Ala Phe Glu Ser His Ser Thr Val 4835 4840 4845		
Ser Ala Tyr Pro Glu Pro Ser Lys Val Thr Ser Pro Asn Val Thr 4850 4855 4860		
Thr Ser Thr Met Glu Asp Thr Thr Ile Ser Arg Ser Ile Pro Lys 4865 4870 4875		
Ser Ser Lys Thr Thr Arg Thr Glu Thr Glu Thr Thr Ser Ser Leu 4880 4885 4890		
Thr Pro Lys Leu Arg Glu Thr Ser Ile Ser Gln Glu Ile Thr Ser 4895 4900 4905		
Ser Thr Glu Thr Ser Thr Val Pro Tyr Lys Glu Leu Thr Gly Ala 4910 4915 4920		
Thr Thr Glu Val Ser Arg Thr Asp Val Thr Ser Ser Ser Ser Thr 4925 4930 4935		
Ser Phe Pro Gly Pro Asp Gln Ser Thr Val Ser Leu Asp Ile Ser 4940 4945 4950		





-continued

Met	Thr	Ser	Pro	Ser	Pro	Val	Ser	Ser	Thr	Ser	Pro	Gln	Ser	Ile
5345						5350					5355			
Pro	Ser	Ser	Pro	Leu	Pro	Val	Thr	Ala	Leu	Pro	Thr	Ser	Val	Leu
5360						5365					5370			
Val	Thr	Thr	Thr	Asp	Val	Leu	Gly	Thr	Thr	Ser	Pro	Glu	Ser	Val
5375						5380					5385			
Thr	Ser	Ser	Pro	Pro	Asn	Leu	Ser	Ser	Ile	Thr	His	Glu	Arg	Pro
5390						5395					5400			
Ala	Thr	Tyr	Lys	Asp	Thr	Ala	His	Thr	Glu	Ala	Ala	Met	His	His
5405						5410					5415			
Ser	Thr	Asn	Thr	Ala	Val	Thr	Asn	Val	Gly	Thr	Ser	Gly	Ser	Gly
5420						5425					5430			
His	Lys	Ser	Gln	Ser	Ser	Val	Leu	Ala	Asp	Ser	Glu	Thr	Ser	Lys
5435						5440					5445			
Ala	Thr	Pro	Leu	Met	Ser	Thr	Thr	Ser	Thr	Leu	Gly	Asp	Thr	Ser
5450						5455					5460			
Val	Ser	Thr	Ser	Thr	Pro	Asn	Ile	Ser	Gln	Thr	Asn	Gln	Ile	Gln
5465						5470					5475			
Thr	Glu	Pro	Thr	Ala	Ser	Leu	Ser	Pro	Arg	Leu	Arg	Glu	Ser	Ser
5480						5485					5490			
Thr	Ser	Glu	Lys	Thr	Ser	Ser	Thr	Thr	Glu	Thr	Asn	Thr	Ala	Phe
5495						5500					5505			
Ser	Tyr	Val	Pro	Thr	Gly	Ala	Ile	Thr	Gln	Ala	Ser	Arg	Thr	Glu
5510						5515					5520			
Ile	Ser	Ser	Ser	Arg	Thr	Ser	Ile	Ser	Asp	Leu	Asp	Arg	Pro	Thr
5525						5530					5535			
Ile	Ala	Pro	Asp	Ile	Ser	Thr	Gly	Met	Ile	Thr	Arg	Leu	Phe	Thr
5540						5545					5550			
Ser	Pro	Ile	Met	Thr	Lys	Ser	Ala	Glu	Met	Thr	Val	Thr	Thr	Gln
5555						5560					5565			
Thr	Thr	Thr	Pro	Gly	Ala	Thr	Ser	Gln	Gly	Ile	Leu	Pro	Trp	Asp
5570						5575					5580			
Thr	Ser	Thr	Thr	Leu	Phe	Gln	Gly	Gly	Thr	His	Ser	Thr	Val	Ser
5585						5590					5595			
Gln	Gly	Phe	Pro	His	Ser	Glu	Ile	Thr	Thr	Leu	Arg	Ser	Arg	Thr
5600						5605					5610			
Pro	Gly	Asp	Val	Ser	Trp	Met	Thr	Thr	Pro	Pro	Val	Glu	Glu	Thr
5615						5620					5625			
Ser	Ser	Gly	Phe	Ser	Leu	Met	Ser	Pro	Ser	Met	Thr	Ser	Pro	Ser
5630						5635					5640			
Pro	Val	Ser	Ser	Thr	Ser	Pro	Glu	Ser	Ile	Pro	Ser	Ser	Pro	Leu
5645						5650					5655			
Pro	Val	Thr	Ala	Leu	Leu	Thr	Ser	Val	Leu	Val	Thr	Thr	Thr	Asn
5660						5665					5670			
Val	Leu	Gly	Thr	Thr	Ser	Pro	Glu	Pro	Val	Thr	Ser	Ser	Pro	Pro
5675						5680					5685			
Asn	Leu	Ser	Ser	Pro	Thr	Gln	Glu	Arg	Leu	Thr	Thr	Tyr	Lys	Asp
5690						5695					5700			
Thr	Ala	His	Thr	Glu	Ala	Met	His	Ala	Ser	Met	His	Thr	Asn	Thr
5705						5710					5715			
Ala	Val	Ala	Asn	Val	Gly	Thr	Ser	Ile	Ser	Gly	His	Glu	Ser	Gln
5720						5725					5730			
Ser	Ser	Val	Pro	Ala	Asp	Ser	His	Thr	Ser	Lys	Ala	Thr	Ser	Pro

-continued

---

5735	5740	5745
Met Gly Ile Thr Phe Ala Met Gly Asp Thr Ser Val Ser Thr Ser 5750 5755 5760		
Thr Pro Ala Phe Phe Glu Thr Arg Ile Gln Thr Glu Ser Thr Ser 5765 5770 5775		
Ser Leu Ile Pro Gly Leu Arg Asp Thr Arg Thr Ser Glu Glu Ile 5780 5785 5790		
Asn Thr Val Thr Glu Thr Ser Thr Val Leu Ser Glu Val Pro Thr 5795 5800 5805		
Thr Thr Thr Thr Glu Val Ser Arg Thr Glu Val Ile Thr Ser Ser 5810 5815 5820		
Arg Thr Thr Ile Ser Gly Pro Asp His Ser Lys Met Ser Pro Tyr 5825 5830 5835		
Ile Ser Thr Glu Thr Ile Thr Arg Leu Ser Thr Phe Pro Phe Val 5840 5845 5850		
Thr Gly Ser Thr Glu Met Ala Ile Thr Asn Gln Thr Gly Pro Ile 5855 5860 5865		
Gly Thr Ile Ser Gln Ala Thr Leu Thr Leu Asp Thr Ser Ser Thr 5870 5875 5880		
Ala Ser Trp Glu Gly Thr His Ser Pro Val Thr Gln Arg Phe Pro 5885 5890 5895		
His Ser Glu Glu Thr Thr Thr Met Ser Arg Ser Thr Lys Gly Val 5900 5905 5910		
Ser Trp Gln Ser Pro Pro Ser Val Glu Glu Thr Ser Ser Pro Ser 5915 5920 5925		
Ser Pro Val Pro Leu Pro Ala Ile Thr Ser His Ser Ser Leu Tyr 5930 5935 5940		
Ser Ala Val Ser Gly Ser Ser Pro Thr Ser Ala Leu Pro Val Thr 5945 5950 5955		
Ser Leu Leu Thr Ser Gly Arg Arg Lys Thr Ile Asp Met Leu Asp 5960 5965 5970		
Thr His Ser Glu Leu Val Thr Ser Ser Leu Pro Ser Ala Ser Ser 5975 5980 5985		
Phe Ser Gly Glu Ile Leu Thr Ser Glu Ala Ser Thr Asn Thr Glu 5990 5995 6000		
Thr Ile His Phe Ser Glu Asn Thr Ala Glu Thr Asn Met Gly Thr 6005 6010 6015		
Thr Asn Ser Met His Lys Leu His Ser Ser Val Ser Ile His Ser 6020 6025 6030		
Gln Pro Ser Gly His Thr Pro Pro Lys Val Thr Gly Ser Met Met 6035 6040 6045		
Glu Asp Ala Ile Val Ser Thr Ser Thr Pro Gly Ser Pro Glu Thr 6050 6055 6060		
Lys Asn Val Asp Arg Asp Ser Thr Ser Pro Leu Thr Pro Glu Leu 6065 6070 6075		
Lys Glu Asp Ser Thr Ala Leu Val Met Asn Ser Thr Thr Glu Ser 6080 6085 6090		
Asn Thr Val Phe Ser Ser Val Ser Leu Asp Ala Ala Thr Glu Val 6095 6100 6105		
Ser Arg Ala Glu Val Thr Tyr Tyr Asp Pro Thr Phe Met Pro Ala 6110 6115 6120		
Ser Ala Gln Ser Thr Lys Ser Pro Asp Ile Ser Pro Glu Ala Ser 6125 6130 6135		

-continued

---

Ser	Ser	His	Ser	Asn	Ser	Pro	Pro	Leu	Thr	Ile	Ser	Thr	His	Lys
6140						6145					6150			
Thr	Ile	Ala	Thr	Gln	Thr	Gly	Pro	Ser	Gly	Val	Thr	Ser	Leu	Gly
6155						6160					6165			
Gln	Leu	Thr	Leu	Asp	Thr	Ser	Thr	Ile	Ala	Thr	Ser	Ala	Gly	Thr
6170						6175					6180			
Pro	Ser	Ala	Arg	Thr	Gln	Asp	Phe	Val	Asp	Ser	Glu	Thr	Thr	Ser
6185						6190					6195			
Val	Met	Asn	Asn	Asp	Leu	Asn	Asp	Val	Leu	Lys	Thr	Ser	Pro	Phe
6200						6205					6210			
Ser	Ala	Glu	Glu	Ala	Asn	Ser	Leu	Ser	Ser	Gln	Ala	Pro	Leu	Leu
6215						6220					6225			
Val	Thr	Thr	Ser	Pro	Ser	Pro	Val	Thr	Ser	Thr	Leu	Gln	Glu	His
6230						6235					6240			
Ser	Thr	Ser	Ser	Leu	Val	Ser	Val	Thr	Ser	Val	Pro	Thr	Pro	Thr
6245						6250					6255			
Leu	Ala	Lys	Ile	Thr	Asp	Met	Asp	Thr	Asn	Leu	Glu	Pro	Val	Thr
6260						6265					6270			
Arg	Ser	Pro	Gln	Asn	Leu	Arg	Asn	Thr	Leu	Ala	Thr	Ser	Glu	Ala
6275						6280					6285			
Thr	Thr	Asp	Thr	His	Thr	Met	His	Pro	Ser	Ile	Asn	Thr	Ala	Val
6290						6295					6300			
Ala	Asn	Val	Gly	Thr	Thr	Ser	Ser	Pro	Asn	Glu	Phe	Tyr	Phe	Thr
6305						6310					6315			
Val	Ser	Pro	Asp	Ser	Asp	Pro	Tyr	Lys	Ala	Thr	Ser	Ala	Val	Val
6320						6325					6330			
Ile	Thr	Ser	Thr	Ser	Gly	Asp	Ser	Ile	Val	Ser	Thr	Ser	Met	Pro
6335						6340					6345			
Arg	Ser	Ser	Ala	Met	Lys	Lys	Ile	Glu	Ser	Glu	Thr	Thr	Phe	Ser
6350						6355					6360			
Leu	Ile	Phe	Arg	Leu	Arg	Glu	Thr	Ser	Thr	Ser	Gln	Lys	Ile	Gly
6365						6370					6375			
Ser	Ser	Ser	Asp	Thr	Ser	Thr	Val	Phe	Asp	Lys	Ala	Phe	Thr	Ala
6380						6385					6390			
Ala	Thr	Thr	Glu	Val	Ser	Arg	Thr	Glu	Leu	Thr	Ser	Ser	Ser	Arg
6395						6400					6405			
Thr	Ser	Ile	Gln	Gly	Thr	Glu	Lys	Pro	Thr	Met	Ser	Pro	Asp	Thr
6410						6415					6420			
Ser	Thr	Arg	Ser	Val	Thr	Met	Leu	Ser	Thr	Phe	Ala	Gly	Leu	Thr
6425						6430					6435			
Lys	Ser	Glu	Glu	Arg	Thr	Ile	Ala	Thr	Gln	Thr	Gly	Pro	His	Arg
6440						6445					6450			
Ala	Thr	Ser	Gln	Gly	Thr	Leu	Thr	Trp	Asp	Thr	Ser	Ile	Thr	Thr
6455						6460					6465			
Ser	Gln	Ala	Gly	Thr	His	Ser	Ala	Met	Thr	His	Gly	Phe	Ser	Gln
6470						6475					6480			
Leu	Asp	Leu	Ser	Thr	Leu	Thr	Ser	Arg	Val	Pro	Glu	Tyr	Ile	Ser
6485						6490					6495			
Gly	Thr	Ser	Pro	Pro	Ser	Val	Glu	Lys	Thr	Ser	Ser	Ser	Ser	Ser
6500						6505					6510			
Leu	Leu	Ser	Leu	Pro	Ala	Ile	Thr	Ser	Pro	Ser	Pro	Val	Pro	Thr
6515						6520					6525			

-continued

Thr	Leu	Pro	Glu	Ser	Arg	Pro	Ser	Ser	Pro	Val	His	Leu	Thr	Ser
6530						6535					6540			
Leu	Pro	Thr	Ser	Gly	Leu	Val	Lys	Thr	Thr	Asp	Met	Leu	Ala	Ser
6545						6550					6555			
Val	Ala	Ser	Leu	Pro	Pro	Asn	Leu	Gly	Ser	Thr	Ser	His	Lys	Ile
6560						6565					6570			
Pro	Thr	Thr	Ser	Glu	Asp	Ile	Lys	Asp	Thr	Glu	Lys	Met	Tyr	Pro
6575						6580					6585			
Ser	Thr	Asn	Ile	Ala	Val	Thr	Asn	Val	Gly	Thr	Thr	Thr	Ser	Glu
6590						6595					6600			
Lys	Glu	Ser	Tyr	Ser	Ser	Val	Pro	Ala	Tyr	Ser	Glu	Pro	Pro	Lys
6605						6610					6615			
Val	Thr	Ser	Pro	Met	Val	Thr	Ser	Phe	Asn	Ile	Arg	Asp	Thr	Ile
6620						6625					6630			
Val	Ser	Thr	Ser	Met	Pro	Gly	Ser	Ser	Glu	Ile	Thr	Arg	Ile	Glu
6635						6640					6645			
Met	Glu	Ser	Thr	Phe	Ser	Leu	Ala	His	Gly	Leu	Lys	Gly	Thr	Ser
6650						6655					6660			
Thr	Ser	Gln	Asp	Pro	Ile	Val	Ser	Thr	Glu	Lys	Ser	Ala	Val	Leu
6665						6670					6675			
His	Lys	Leu	Thr	Thr	Gly	Ala	Thr	Glu	Thr	Ser	Arg	Thr	Glu	Val
6680						6685					6690			
Ala	Ser	Ser	Arg	Arg	Thr	Ser	Ile	Pro	Gly	Pro	Asp	His	Ser	Thr
6695						6700					6705			
Glu	Ser	Pro	Asp	Ile	Ser	Thr	Glu	Val	Ile	Pro	Ser	Leu	Pro	Ile
6710						6715					6720			
Ser	Leu	Gly	Ile	Thr	Glu	Ser	Ser	Asn	Met	Thr	Ile	Ile	Thr	Arg
6725						6730					6735			
Thr	Gly	Pro	Pro	Leu	Gly	Ser	Thr	Ser	Gln	Gly	Thr	Phe	Thr	Leu
6740						6745					6750			
Asp	Thr	Pro	Thr	Thr	Ser	Ser	Arg	Ala	Gly	Thr	His	Ser	Met	Ala
6755						6760					6765			
Thr	Gln	Glu	Phe	Pro	His	Ser	Glu	Met	Thr	Thr	Val	Met	Asn	Lys
6770						6775					6780			
Asp	Pro	Glu	Ile	Leu	Ser	Trp	Thr	Ile	Pro	Pro	Ser	Ile	Glu	Lys
6785						6790					6795			
Thr	Ser	Phe	Ser	Ser	Ser	Leu	Met	Pro	Ser	Pro	Ala	Met	Thr	Ser
6800						6805					6810			
Pro	Pro	Val	Ser	Ser	Thr	Leu	Pro	Lys	Thr	Ile	His	Thr	Thr	Pro
6815						6820					6825			
Ser	Pro	Met	Thr	Ser	Leu	Leu	Thr	Pro	Ser	Leu	Val	Met	Thr	Thr
6830						6835					6840			
Asp	Thr	Leu	Gly	Thr	Ser	Pro	Glu	Pro	Thr	Thr	Ser	Ser	Pro	Pro
6845						6850					6855			
Asn	Leu	Ser	Ser	Thr	Ser	His	Glu	Ile	Leu	Thr	Thr	Asp	Glu	Asp
6860						6865					6870			
Thr	Thr	Ala	Ile	Glu	Ala	Met	His	Pro	Ser	Thr	Ser	Thr	Ala	Ala
6875						6880					6885			
Thr	Asn	Val	Glu	Thr	Thr	Ser	Ser	Gly	His	Gly	Ser	Gln	Ser	Ser
6890						6895					6900			
Val	Leu	Ala	Asp	Ser	Glu	Lys	Thr	Lys	Ala	Thr	Ala	Pro	Met	Asp
6905						6910					6915			
Thr	Thr	Ser	Thr	Met	Gly	His	Thr	Thr	Val	Ser	Thr	Ser	Met	Ser

-continued

6920	6925	6930
Val Ser Ser Glu Thr Thr Lys Ile Lys Arg Glu Ser Thr Tyr Ser 6935 6940 6945		
Leu Thr Pro Gly Leu Arg Glu Thr Ser Ile Ser Gln Asn Ala Ser 6950 6955 6960		
Phe Ser Thr Asp Thr Ser Ile Val Leu Ser Glu Val Pro Thr Gly 6965 6970 6975		
Thr Thr Ala Glu Val Ser Arg Thr Glu Val Thr Ser Ser Gly Arg 6980 6985 6990		
Thr Ser Ile Pro Gly Pro Ser Gln Ser Thr Val Leu Pro Glu Ile 6995 7000 7005		
Ser Thr Arg Thr Met Thr Arg Leu Phe Ala Ser Pro Thr Met Thr 7010 7015 7020		
Glu Ser Ala Glu Met Thr Ile Pro Thr Gln Thr Gly Pro Ser Gly 7025 7030 7035		
Ser Thr Ser Gln Asp Thr Leu Thr Leu Asp Thr Ser Thr Thr Lys 7040 7045 7050		
Ser Gln Ala Lys Thr His Ser Thr Leu Thr Gln Arg Phe Pro His 7055 7060 7065		
Ser Glu Met Thr Thr Leu Met Ser Arg Gly Pro Gly Asp Met Ser 7070 7075 7080		
Trp Gln Ser Ser Pro Ser Leu Glu Asn Pro Ser Ser Leu Pro Ser 7085 7090 7095		
Leu Leu Ser Leu Pro Ala Thr Thr Ser Pro Pro Pro Ile Ser Ser 7100 7105 7110		
Thr Leu Pro Val Thr Ile Ser Ser Ser Pro Leu Pro Val Thr Ser 7115 7120 7125		
Leu Leu Thr Ser Ser Pro Val Thr Thr Thr Asp Met Leu His Thr 7130 7135 7140		
Ser Pro Glu Leu Val Thr Ser Ser Pro Pro Lys Leu Ser His Thr 7145 7150 7155		
Ser Asp Glu Arg Leu Thr Thr Gly Lys Asp Thr Thr Asn Thr Glu 7160 7165 7170		
Ala Val His Pro Ser Thr Asn Thr Ala Ala Ser Asn Val Glu Ile 7175 7180 7185		
Pro Ser Ser Gly His Glu Ser Pro Ser Ser Ala Leu Ala Asp Ser 7190 7195 7200		
Glu Thr Ser Lys Ala Thr Ser Pro Met Phe Ile Thr Ser Thr Gln 7205 7210 7215		
Glu Asp Thr Thr Val Ala Ile Ser Thr Pro His Phe Leu Glu Thr 7220 7225 7230		
Ser Arg Ile Gln Lys Glu Ser Ile Ser Ser Leu Ser Pro Lys Leu 7235 7240 7245		
Arg Glu Thr Gly Ser Ser Val Glu Thr Ser Ser Ala Ile Glu Thr 7250 7255 7260		
Ser Ala Val Leu Ser Glu Val Ser Ile Gly Ala Thr Thr Glu Ile 7265 7270 7275		
Ser Arg Thr Glu Val Thr Ser Ser Ser Arg Thr Ser Ile Ser Gly 7280 7285 7290		
Ser Ala Glu Ser Thr Met Leu Pro Glu Ile Ser Thr Thr Arg Lys 7295 7300 7305		
Ile Ile Lys Phe Pro Thr Ser Pro Ile Leu Ala Glu Ser Ser Glu 7310 7315 7320		

-continued

---

Met Thr	Ile Lys Thr Gln	Thr Ser Pro Pro Gly	Ser Thr Ser Glu
7325		7330	7335
Ser Thr	Phe Thr Leu Asp	Thr Ser Thr Thr Pro	Ser Leu Val Ile
7340		7345	7350
Thr His	Ser Thr Met Thr	Gln Arg Leu Pro His	Ser Glu Ile Thr
7355		7360	7365
Thr Leu	Val Ser Arg Gly	Ala Gly Asp Val Pro	Arg Pro Ser Ser
7370		7375	7380
Leu Pro	Val Glu Glu Thr	Ser Pro Pro Ser Ser	Gln Leu Ser Leu
7385		7390	7395
Ser Ala	Met Ile Ser Pro	Ser Pro Val Ser Ser	Thr Leu Pro Ala
7400		7405	7410
Ser Ser	His Ser Ser Ser	Ala Ser Val Thr Ser	Leu Leu Thr Pro
7415		7420	7425
Gly Gln	Val Lys Thr Thr	Glu Val Leu Asp Ala	Ser Ala Glu Pro
7430		7435	7440
Glu Thr	Ser Ser Pro Pro	Ser Leu Ser Ser Thr	Ser Val Glu Ile
7445		7450	7455
Leu Ala	Thr Ser Glu Val	Thr Thr Asp Thr Glu	Lys Ile His Pro
7460		7465	7470
Phe Ser	Asn Thr Ala Val	Thr Lys Val Gly Thr	Ser Ser Ser Gly
7475		7480	7485
His Glu	Ser Pro Ser Ser	Val Leu Pro Asp Ser	Glu Thr Thr Lys
7490		7495	7500
Ala Thr	Ser Ala Met Gly	Thr Ile Ser Ile Met	Gly Asp Thr Ser
7505		7510	7515
Val Ser	Thr Leu Thr Pro	Ala Leu Ser Asn Thr	Arg Lys Ile Gln
7520		7525	7530
Ser Glu	Pro Ala Ser Ser	Leu Thr Thr Arg Leu	Arg Glu Thr Ser
7535		7540	7545
Thr Ser	Glu Glu Thr Ser	Leu Ala Thr Glu Ala	Asn Thr Val Leu
7550		7555	7560
Ser Lys	Val Ser Thr Gly	Ala Thr Thr Glu Val	Ser Arg Thr Glu
7565		7570	7575
Ala Ile	Ser Phe Ser Arg	Thr Ser Met Ser Gly	Pro Glu Gln Ser
7580		7585	7590
Thr Met	Ser Gln Asp Ile	Ser Ile Gly Thr Ile	Pro Arg Ile Ser
7595		7600	7605
Ala Ser	Ser Val Leu Thr	Glu Ser Ala Lys Met	Thr Ile Thr Thr
7610		7615	7620
Gln Thr	Gly Pro Ser Glu	Ser Thr Leu Glu Ser	Thr Leu Asn Leu
7625		7630	7635
Asn Thr	Ala Thr Thr Pro	Ser Trp Val Glu Thr	His Ser Ile Val
7640		7645	7650
Ile Gln	Gly Phe Pro His	Pro Glu Met Thr Thr	Ser Met Gly Arg
7655		7660	7665
Gly Pro	Gly Gly Val Ser	Trp Pro Ser Pro Pro	Phe Val Lys Glu
7670		7675	7680
Thr Ser	Pro Pro Ser Ser	Pro Leu Ser Leu Pro	Ala Val Thr Ser
7685		7690	7695
Pro His	Pro Val Ser Thr	Thr Phe Leu Ala His	Ile Pro Pro Ser
7700		7705	7710

-continued

Pro	Leu	Pro	Val	Thr	Ser	Leu	Leu	Thr	Ser	Gly	Pro	Ala	Thr	Thr
7715						7720					7725			
Thr	Asp	Ile	Leu	Gly	Thr	Ser	Thr	Glu	Pro	Gly	Thr	Ser	Ser	Ser
7730						7735					7740			
Ser	Ser	Leu	Ser	Thr	Thr	Ser	His	Glu	Arg	Leu	Thr	Thr	Tyr	Lys
7745						7750					7755			
Asp	Thr	Ala	His	Thr	Glu	Ala	Val	His	Pro	Ser	Thr	Asn	Thr	Gly
7760						7765					7770			
Gly	Thr	Asn	Val	Ala	Thr	Thr	Ser	Ser	Gly	Tyr	Lys	Ser	Gln	Ser
7775						7780					7785			
Ser	Val	Leu	Ala	Asp	Ser	Ser	Pro	Met	Cys	Thr	Thr	Ser	Thr	Met
7790						7795					7800			
Gly	Asp	Thr	Ser	Val	Leu	Thr	Ser	Thr	Pro	Ala	Phe	Leu	Glu	Thr
7805						7810					7815			
Arg	Arg	Ile	Gln	Thr	Glu	Leu	Ala	Ser	Ser	Leu	Thr	Pro	Gly	Leu
7820						7825					7830			
Arg	Glu	Ser	Ser	Gly	Ser	Glu	Gly	Thr	Ser	Ser	Gly	Thr	Lys	Met
7835						7840					7845			
Ser	Thr	Val	Leu	Ser	Lys	Val	Pro	Thr	Gly	Ala	Thr	Thr	Glu	Ile
7850						7855					7860			
Ser	Lys	Glu	Asp	Val	Thr	Ser	Ile	Pro	Gly	Pro	Ala	Gln	Ser	Thr
7865						7870					7875			
Ile	Ser	Pro	Asp	Ile	Ser	Thr	Arg	Thr	Val	Ser	Trp	Phe	Ser	Thr
7880						7885					7890			
Ser	Pro	Val	Met	Thr	Glu	Ser	Ala	Glu	Ile	Thr	Met	Asn	Thr	His
7895						7900					7905			
Thr	Ser	Pro	Leu	Gly	Ala	Thr	Thr	Gln	Gly	Thr	Ser	Thr	Leu	Asp
7910						7915					7920			
Thr	Ser	Ser	Thr	Thr	Ser	Leu	Thr	Met	Thr	His	Ser	Thr	Ile	Ser
7925						7930					7935			
Gln	Gly	Phe	Ser	His	Ser	Gln	Met	Ser	Thr	Leu	Met	Arg	Arg	Gly
7940						7945					7950			
Pro	Glu	Asp	Val	Ser	Trp	Met	Ser	Pro	Pro	Leu	Leu	Glu	Lys	Thr
7955						7960					7965			
Arg	Pro	Ser	Phe	Ser	Leu	Met	Ser	Ser	Pro	Ala	Thr	Thr	Ser	Pro
7970						7975					7980			
Ser	Pro	Val	Ser	Ser	Thr	Leu	Pro	Glu	Ser	Ile	Ser	Ser	Ser	Pro
7985						7990					7995			
Leu	Pro	Val	Thr	Ser	Leu	Leu	Thr	Ser	Gly	Leu	Ala	Lys	Thr	Thr
8000						8005					8010			
Asp	Met	Leu	His	Lys	Ser	Ser	Glu	Pro	Val	Thr	Asn	Ser	Pro	Ala
8015						8020					8025			
Asn	Leu	Ser	Ser	Thr	Ser	Val	Glu	Ile	Leu	Ala	Thr	Ser	Glu	Val
8030						8035					8040			
Thr	Thr	Asp	Thr	Glu	Lys	Thr	His	Pro	Ser	Ser	Asn	Arg	Thr	Val
8045						8050					8055			
Thr	Asp	Val	Gly	Thr	Ser	Ser	Ser	Gly	His	Glu	Ser	Thr	Ser	Phe
8060						8065					8070			
Val	Leu	Ala	Asp	Ser	Gln	Thr	Ser	Lys	Val	Thr	Ser	Pro	Met	Val
8075						8080					8085			
Ile	Thr	Ser	Thr	Met	Glu	Asp	Thr	Ser	Val	Ser	Thr	Ser	Thr	Pro
8090						8095					8100			
Gly	Phe	Phe	Glu	Thr	Ser	Arg	Ile	Gln	Thr	Glu	Pro	Thr	Ser	Ser



-continued

---

8105		8110		8115
Leu Thr	Leu Gly	Leu Arg	Lys Thr	Ser Ser Ser Glu Gly Thr Ser
8120		8125		8130
Leu Ala	Thr Glu	Met Ser	Thr Val	Leu Ser Gly Val Pro Thr Gly
8135		8140		8145
Ala Thr	Ala Glu	Val Ser	Arg Thr	Glu Val Thr Ser Ser Ser Arg
8150		8155		8160
Thr Ser	Ile Ser	Gly Phe	Ala Gln	Leu Thr Val Ser Pro Glu Thr
8165		8170		8175
Ser Thr	Glu Thr	Ile Thr	Arg Leu	Pro Thr Ser Ser Ile Met Thr
8180		8185		8190
Glu Ser	Ala Glu	Met Met	Ile Lys	Thr Gln Thr Asp Pro Pro Gly
8195		8200		8205
Ser Thr	Pro Glu	Ser Thr	His Thr	Val Asp Ile Ser Thr Thr Pro
8210		8215		8220
Asn Trp	Val Glu	Thr His	Ser Thr	Val Thr Gln Arg Phe Ser His
8225		8230		8235
Ser Glu	Met Thr	Thr Leu	Val Ser	Arg Ser Pro Gly Asp Met Leu
8240		8245		8250
Trp Pro	Ser Gln	Ser Ser	Val Glu	Glu Thr Ser Ser Ala Ser Ser
8255		8260		8265
Leu Leu	Ser Leu	Pro Ala	Thr Thr	Ser Pro Ser Pro Val Ser Ser
8270		8275		8280
Thr Leu	Val Glu	Asp Phe	Pro Ser	Ala Ser Leu Pro Val Thr Ser
8285		8290		8295
Leu Leu	Asn Pro	Gly Leu	Val Ile	Thr Thr Asp Arg Met Gly Ile
8300		8305		8310
Ser Arg	Glu Pro	Gly Thr	Ser Ser	Thr Ser Asn Leu Ser Ser Thr
8315		8320		8325
Ser His	Glu Arg	Leu Thr	Thr Leu	Glu Asp Thr Val Asp Thr Glu
8330		8335		8340
Asp Met	Gln Pro	Ser Thr	His Thr	Ala Val Thr Asn Val Arg Thr
8345		8350		8355
Ser Ile	Ser Gly	His Glu	Ser Gln	Ser Ser Val Leu Ser Asp Ser
8360		8365		8370
Glu Thr	Pro Lys	Ala Thr	Ser Pro	Met Gly Thr Thr Tyr Thr Met
8375		8380		8385
Gly Glu	Thr Ser	Val Ser	Ile Ser	Thr Ser Asp Phe Phe Glu Thr
8390		8395		8400
Ser Arg	Ile Gln	Ile Glu	Pro Thr	Ser Ser Leu Thr Ser Gly Leu
8405		8410		8415
Arg Glu	Thr Ser	Ser Ser	Glu Arg	Ile Ser Ser Ala Thr Glu Gly
8420		8425		8430
Ser Thr	Val Leu	Ser Glu	Val Pro	Ser Gly Ala Thr Thr Glu Val
8435		8440		8445
Ser Arg	Thr Glu	Val Ile	Ser Ser	Arg Gly Thr Ser Met Ser Gly
8450		8455		8460
Pro Asp	Gln Phe	Thr Ile	Ser Pro	Asp Ile Ser Thr Glu Ala Ile
8465		8470		8475
Thr Arg	Leu Ser	Thr Ser	Pro Ile	Met Thr Glu Ser Ala Glu Ser
8480		8485		8490
Ala Ile	Thr Ile	Glu Thr	Gly Ser	Pro Gly Ala Thr Ser Glu Gly
8495		8500		8505

-continued

---

Thr Leu	Thr Leu Asp	Thr Ser	Thr Thr Thr	Phe Trp	Ser Gly Thr
8510		8515		8520	
His Ser	Thr Ala Ser	Pro Gly	Phe Ser His Ser	Glu Met Thr Thr	
8525		8530		8535	
Leu Met	Ser Arg Thr	Pro Gly	Asp Val Pro Trp	Pro Ser Leu Pro	
8540		8545		8550	
Ser Val	Glu Glu Ala	Ser Ser	Val Ser Ser Ser	Leu Ser Ser Pro	
8555		8560		8565	
Ala Met	Thr Ser Thr	Ser Phe	Phe Ser Thr Leu	Pro Glu Ser Ile	
8570		8575		8580	
Ser Ser	Ser Pro His	Pro Val	Thr Ala Leu Leu	Thr Leu Gly Pro	
8585		8590		8595	
Val Lys	Thr Thr Asp	Met Leu	Arg Thr Ser Ser	Glu Pro Glu Thr	
8600		8605		8610	
Ser Ser	Pro Pro Asn	Leu Ser	Ser Thr Ser Ala	Glu Ile Leu Ala	
8615		8620		8625	
Thr Ser	Glu Val Thr	Lys Asp	Arg Glu Lys Ile	His Pro Ser Ser	
8630		8635		8640	
Asn Thr	Pro Val Val	Asn Val	Gly Thr Val Ile	Tyr Lys His Leu	
8645		8650		8655	
Ser Pro	Ser Ser Val	Leu Ala	Asp Leu Val Thr	Thr Lys Pro Thr	
8660		8665		8670	
Ser Pro	Met Ala Thr	Thr Ser	Thr Leu Gly Asn	Thr Ser Val Ser	
8675		8680		8685	
Thr Ser	Thr Pro Ala	Phe Pro	Glu Thr Met Met	Thr Gln Pro Thr	
8690		8695		8700	
Ser Ser	Leu Thr Ser	Gly Leu	Arg Glu Ile Ser	Thr Ser Gln Glu	
8705		8710		8715	
Thr Ser	Ser Ala Thr	Glu Arg	Ser Ala Ser Leu	Ser Gly Met Pro	
8720		8725		8730	
Thr Gly	Ala Thr Thr	Lys Val	Ser Arg Thr Glu	Ala Leu Ser Leu	
8735		8740		8745	
Gly Arg	Thr Ser Thr	Pro Gly	Pro Ala Gln Ser	Thr Ile Ser Pro	
8750		8755		8760	
Glu Ile	Ser Thr Glu	Thr Ile	Thr Arg Ile Ser	Thr Pro Leu Thr	
8765		8770		8775	
Thr Thr	Gly Ser Ala	Glu Met	Thr Ile Thr Pro	Lys Thr Gly His	
8780		8785		8790	
Ser Gly	Ala Ser Ser	Gln Gly	Thr Phe Thr Leu	Asp Thr Ser Ser	
8795		8800		8805	
Arg Ala	Ser Trp Pro	Gly Thr	His Ser Ala Ala	Thr His Arg Ser	
8810		8815		8820	
Pro His	Ser Gly Met	Thr Thr	Pro Met Ser Arg	Gly Pro Glu Asp	
8825		8830		8835	
Val Ser	Trp Pro Ser	Arg Pro	Ser Val Glu Lys	Thr Ser Pro Pro	
8840		8845		8850	
Ser Ser	Leu Val Ser	Leu Ser	Ala Val Thr Ser	Pro Ser Pro Leu	
8855		8860		8865	
Tyr Ser	Thr Pro Ser	Glu Ser	Ser His Ser Ser	Pro Leu Arg Val	
8870		8875		8880	
Thr Ser	Leu Phe Thr	Pro Val	Met Met Lys Thr	Thr Asp Met Leu	
8885		8890		8895	

-continued

Asp	Thr	Ser	Leu	Glu	Pro	Val	Thr	Thr	Ser	Pro	Pro	Ser	Met	Asn
8900						8905					8910			
Ile	Thr	Ser	Asp	Glu	Ser	Leu	Ala	Thr	Ser	Lys	Ala	Thr	Met	Glu
8915						8920					8925			
Thr	Glu	Ala	Ile	Gln	Leu	Ser	Glu	Asn	Thr	Ala	Val	Thr	Gln	Met
8930						8935					8940			
Gly	Thr	Ile	Ser	Ala	Arg	Gln	Glu	Phe	Tyr	Ser	Ser	Tyr	Pro	Gly
8945						8950					8955			
Leu	Pro	Glu	Pro	Ser	Lys	Val	Thr	Ser	Pro	Val	Val	Thr	Ser	Ser
8960						8965					8970			
Thr	Ile	Lys	Asp	Ile	Val	Ser	Thr	Thr	Ile	Pro	Ala	Ser	Ser	Glu
8975						8980					8985			
Ile	Thr	Arg	Ile	Glu	Met	Glu	Ser	Thr	Ser	Thr	Leu	Thr	Pro	Thr
8990						8995					9000			
Pro	Arg	Glu	Thr	Ser	Thr	Ser	Gln	Glu	Ile	His	Ser	Ala	Thr	Lys
9005						9010					9015			
Pro	Ser	Thr	Val	Pro	Tyr	Lys	Ala	Leu	Thr	Ser	Ala	Thr	Ile	Glu
9020						9025					9030			
Asp	Ser	Met	Thr	Gln	Val	Met	Ser	Ser	Ser	Arg	Gly	Pro	Ser	Pro
9035						9040					9045			
Asp	Gln	Ser	Thr	Met	Ser	Gln	Asp	Ile	Ser	Thr	Glu	Val	Ile	Thr
9050						9055					9060			
Arg	Leu	Ser	Thr	Ser	Pro	Ile	Lys	Thr	Glu	Ser	Thr	Glu	Met	Thr
9065						9070					9075			
Ile	Thr	Thr	Gln	Thr	Gly	Ser	Pro	Gly	Ala	Thr	Ser	Arg	Gly	Thr
9080						9085					9090			
Leu	Thr	Leu	Asp	Thr	Ser	Thr	Thr	Phe	Met	Ser	Gly	Thr	His	Ser
9095						9100					9105			
Thr	Ala	Ser	Gln	Gly	Phe	Ser	His	Ser	Gln	Met	Thr	Ala	Leu	Met
9110						9115					9120			
Ser	Arg	Thr	Pro	Gly	Asp	Val	Pro	Trp	Leu	Ser	His	Pro	Ser	Val
9125						9130					9135			
Glu	Glu	Ala	Ser	Ser	Ala	Ser	Phe	Ser	Leu	Ser	Ser	Pro	Val	Met
9140						9145					9150			
Thr	Ser	Ser	Ser	Pro	Val	Ser	Ser	Thr	Leu	Pro	Asp	Ser	Ile	His
9155						9160					9165			
Ser	Ser	Ser	Leu	Pro	Val	Thr	Ser	Leu	Leu	Thr	Ser	Gly	Leu	Val
9170						9175					9180			
Lys	Thr	Thr	Glu	Leu	Leu	Gly	Thr	Ser	Ser	Glu	Pro	Glu	Thr	Ser
9185						9190					9195			
Ser	Pro	Pro	Asn	Leu	Ser	Ser	Thr	Ser	Ala	Glu	Ile	Leu	Ala	Ile
9200						9205					9210			
Thr	Glu	Val	Thr	Thr	Asp	Thr	Glu	Lys	Leu	Glu	Met	Thr	Asn	Val
9215						9220					9225			
Val	Thr	Ser	Gly	Tyr	Thr	His	Glu	Ser	Pro	Ser	Ser	Val	Leu	Ala
9230						9235					9240			
Asp	Ser	Val	Thr	Thr	Lys	Ala	Thr	Ser	Ser	Met	Gly	Ile	Thr	Tyr
9245						9250					9255			
Pro	Thr	Gly	Asp	Thr	Asn	Val	Leu	Thr	Ser	Thr	Pro	Ala	Phe	Ser
9260						9265					9270			
Asp	Thr	Ser	Arg	Ile	Gln	Thr	Lys	Ser	Lys	Leu	Ser	Leu	Thr	Pro
9275						9280					9285			
Gly	Leu	Met	Glu	Thr	Ser	Ile	Ser	Glu	Glu	Thr	Ser	Ser	Ala	Thr

-continued

---

9290		9295		9300
Glu Lys Ser Thr Val Leu Ser Ser Val Pro Thr Gly Ala Thr Thr 9305		9310		9315
Glu Val Ser Arg Thr Glu Ala Ile Ser Ser Ser Arg Thr Ser Ile 9320		9325		9330
Pro Gly Pro Ala Gln Ser Thr Met Ser Ser Asp Thr Ser Met Glu 9335		9340		9345
Thr Ile Thr Arg Ile Ser Thr Pro Leu Thr Arg Lys Glu Ser Thr 9350		9355		9360
Asp Met Ala Ile Thr Pro Lys Thr Gly Pro Ser Gly Ala Thr Ser 9365		9370		9375
Gln Gly Thr Phe Thr Leu Asp Ser Ser Ser Thr Ala Ser Trp Pro 9380		9385		9390
Gly Thr His Ser Ala Thr Thr Gln Arg Phe Pro Gln Ser Val Val 9395		9400		9405
Thr Thr Pro Met Ser Arg Gly Pro Glu Asp Val Ser Trp Pro Ser 9410		9415		9420
Pro Leu Ser Val Glu Lys Asn Ser Pro Pro Ser Ser Leu Val Ser 9425		9430		9435
Ser Ser Ser Val Thr Ser Pro Ser Pro Leu Tyr Ser Thr Pro Ser 9440		9445		9450
Gly Ser Ser His Ser Ser Pro Val Pro Val Thr Ser Leu Phe Thr 9455		9460		9465
Ser Ile Met Met Lys Ala Thr Asp Met Leu Asp Ala Ser Leu Glu 9470		9475		9480
Pro Glu Thr Thr Ser Ala Pro Asn Met Asn Ile Thr Ser Asp Glu 9485		9490		9495
Ser Leu Ala Ala Ser Lys Ala Thr Thr Glu Thr Glu Ala Ile His 9500		9505		9510
Val Phe Glu Asn Thr Ala Ala Ser His Val Glu Thr Thr Ser Ala 9515		9520		9525
Thr Glu Glu Leu Tyr Ser Ser Ser Pro Gly Phe Ser Glu Pro Thr 9530		9535		9540
Lys Val Ile Ser Pro Val Val Thr Ser Ser Ser Ile Arg Asp Asn 9545		9550		9555
Met Val Ser Thr Thr Met Pro Gly Ser Ser Gly Ile Thr Arg Ile 9560		9565		9570
Glu Ile Glu Ser Met Ser Ser Leu Thr Pro Gly Leu Arg Glu Thr 9575		9580		9585
Arg Thr Ser Gln Asp Ile Thr Ser Ser Thr Glu Thr Ser Thr Val 9590		9595		9600
Leu Tyr Lys Met Pro Ser Gly Ala Thr Pro Glu Val Ser Arg Thr 9605		9610		9615
Glu Val Met Pro Ser Ser Arg Thr Ser Ile Pro Gly Pro Ala Gln 9620		9625		9630
Ser Thr Met Ser Leu Asp Ile Ser Asp Glu Val Val Thr Arg Leu 9635		9640		9645
Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ile Thr Ile Thr 9650		9655		9660
Thr Gln Thr Gly Tyr Ser Leu Ala Thr Ser Gln Val Thr Leu Pro 9665		9670		9675
Leu Gly Thr Ser Met Thr Phe Leu Ser Gly Thr His Ser Thr Met 9680		9685		9690

-continued

---

Ser	Gln	Gly	Leu	Ser	His	Ser	Glu	Met	Thr	Asn	Leu	Met	Ser	Arg
9695						9700					9705			
Gly	Pro	Glu	Ser	Leu	Ser	Trp	Thr	Ser	Pro	Arg	Phe	Val	Glu	Thr
9710						9715					9720			
Thr	Arg	Ser	Ser	Ser	Ser	Leu	Thr	Ser	Leu	Pro	Leu	Thr	Thr	Ser
9725						9730					9735			
Leu	Ser	Pro	Val	Ser	Ser	Thr	Leu	Leu	Asp	Ser	Ser	Pro	Ser	Ser
9740						9745					9750			
Pro	Leu	Pro	Val	Thr	Ser	Leu	Ile	Leu	Pro	Gly	Leu	Val	Lys	Thr
9755						9760					9765			
Thr	Glu	Val	Leu	Asp	Thr	Ser	Ser	Glu	Pro	Lys	Thr	Ser	Ser	Ser
9770						9775					9780			
Pro	Asn	Leu	Ser	Ser	Thr	Ser	Val	Glu	Ile	Pro	Ala	Thr	Ser	Glu
9785						9790					9795			
Ile	Met	Thr	Asp	Thr	Glu	Lys	Ile	His	Pro	Ser	Ser	Asn	Thr	Ala
9800						9805					9810			
Val	Ala	Lys	Val	Arg	Thr	Ser	Ser	Ser	Val	His	Glu	Ser	His	Ser
9815						9820					9825			
Ser	Val	Leu	Ala	Asp	Ser	Glu	Thr	Thr	Ile	Thr	Ile	Pro	Ser	Met
9830						9835					9840			
Gly	Ile	Thr	Ser	Ala	Val	Asp	Asp	Thr	Thr	Val	Phe	Thr	Ser	Asn
9845						9850					9855			
Pro	Ala	Phe	Ser	Glu	Thr	Arg	Arg	Ile	Pro	Thr	Glu	Pro	Thr	Phe
9860						9865					9870			
Ser	Leu	Thr	Pro	Gly	Phe	Arg	Glu	Thr	Ser	Thr	Ser	Glu	Glu	Thr
9875						9880					9885			
Thr	Ser	Ile	Thr	Glu	Thr	Ser	Ala	Val	Leu	Tyr	Gly	Val	Pro	Thr
9890						9895					9900			
Ser	Ala	Thr	Thr	Glu	Val	Ser	Met	Thr	Glu	Ile	Met	Ser	Ser	Asn
9905						9910					9915			
Arg	Ile	His	Ile	Pro	Asp	Ser	Asp	Gln	Ser	Thr	Met	Ser	Pro	Asp
9920						9925					9930			
Ile	Ile	Thr	Glu	Val	Ile	Thr	Arg	Leu	Ser	Ser	Ser	Ser	Met	Met
9935						9940					9945			
Ser	Glu	Ser	Thr	Gln	Met	Thr	Ile	Thr	Thr	Gln	Lys	Ser	Ser	Pro
9950						9955					9960			
Gly	Ala	Thr	Ala	Gln	Ser	Thr	Leu	Thr	Leu	Ala	Thr	Thr	Thr	Ala
9965						9970					9975			
Pro	Leu	Ala	Arg	Thr	His	Ser	Thr	Val	Pro	Pro	Arg	Phe	Leu	His
9980						9985					9990			
Ser	Glu	Met	Thr	Thr	Leu	Met	Ser	Arg	Ser	Pro	Glu	Asn	Pro	Ser
9995						10000					10005			
Trp	Lys	Ser	Ser	Leu	Phe	Val	Glu	Lys	Thr	Ser	Ser	Ser	Ser	Ser
10010						10015					10020			
Leu	Leu	Ser	Leu	Pro	Val	Thr	Thr	Ser	Pro	Ser	Val	Ser	Ser	Thr
10025						10030					10035			
Leu	Pro	Gln	Ser	Ile	Pro	Ser	Ser	Ser	Phe	Ser	Val	Thr	Ser	Leu
10040						10045					10050			
Leu	Thr	Pro	Gly	Met	Val	Lys	Thr	Thr	Asp	Thr	Ser	Thr	Glu	Pro
10055						10060					10065			
Gly	Thr	Ser	Leu	Ser	Pro	Asn	Leu	Ser	Gly	Thr	Ser	Val	Glu	Ile
10070						10075					10080			

-continued

Leu Ala 10085	Ala Ser Glu Val Thr 10090	Thr Asp Thr Glu Lys 10095	Ile His Pro
Ser Ser 10100	Ser Met Ala Val Thr 10105	Asn Val Gly Thr Thr 10110	Ser Ser Gly
His Glu 10115	Leu Tyr Ser Ser Val 10120	Ser Ile His Ser Glu 10125	Pro Ser Lys
Ala Thr 10130	Tyr Pro Val Gly Thr 10135	Pro Ser Ser Met Ala 10140	Glu Thr Ser
Ile Ser 10145	Thr Ser Met Pro Ala 10150	Asn Phe Glu Thr Thr 10155	Gly Phe Glu
Ala Glu 10160	Pro Phe Ser His Leu 10165	Thr Ser Gly Phe Arg 10170	Lys Thr Asn
Met Ser 10175	Leu Asp Thr Ser Ser 10180	Val Thr Pro Thr Asn 10185	Thr Pro Ser
Ser Pro 10190	Gly Ser Thr His Leu 10195	Leu Gln Ser Ser Lys 10200	Thr Asp Phe
Thr Ser 10205	Ser Ala Lys Thr Ser 10210	Ser Pro Asp Trp Pro 10215	Pro Ala Ser
Gln Tyr 10220	Thr Glu Ile Pro Val 10225	Asp Ile Ile Thr Pro 10230	Phe Asn Ala
Ser Pro 10235	Ser Ile Thr Glu Ser 10240	Thr Gly Ile Thr Ser 10245	Phe Pro Glu
Ser Arg 10250	Phe Thr Met Ser Val 10255	Thr Glu Ser Thr His 10260	His Leu Ser
Thr Asp 10265	Leu Leu Pro Ser Ala 10270	Glu Thr Ile Ser Thr 10275	Gly Thr Val
Met Pro 10280	Ser Leu Ser Glu Ala 10285	Met Thr Ser Phe Ala 10290	Thr Thr Gly
Val Pro 10295	Arg Ala Ile Ser Gly 10300	Ser Gly Ser Pro Phe 10305	Ser Arg Thr
Glu Ser 10310	Gly Pro Gly Asp Ala 10315	Thr Leu Ser Thr Ile 10320	Ala Glu Ser
Leu Pro 10325	Ser Ser Thr Pro Val 10330	Pro Phe Ser Ser Ser 10335	Thr Phe Thr
Thr Thr 10340	Asp Ser Ser Thr Ile 10345	Pro Ala Leu His Glu 10350	Ile Thr Ser
Ser Ser 10355	Ala Thr Pro Tyr Arg 10360	Val Asp Thr Ser Leu 10365	Gly Thr Glu
Ser Ser 10370	Thr Thr Glu Gly Arg 10375	Leu Val Met Val Ser 10380	Thr Leu Asp
Thr Ser 10385	Ser Gln Pro Gly Arg 10390	Thr Ser Ser Ser Pro 10395	Ile Leu Asp
Thr Arg 10400	Met Thr Glu Ser Val 10405	Glu Leu Gly Thr Val 10410	Thr Ser Ala
Tyr Gln 10415	Val Pro Ser Leu Ser 10420	Thr Arg Leu Thr Arg 10425	Thr Asp Gly
Ile Met 10430	Glu His Ile Thr Lys 10435	Ile Pro Asn Glu Ala 10440	Ala His Arg
Gly Thr 10445	Ile Arg Pro Val Lys 10450	Gly Pro Gln Thr Ser 10455	Thr Ser Pro
Ala Ser 10460	Pro Lys Gly Leu His 10465	Thr Gly Gly Thr Lys 10470	Arg Met Glu
Thr Thr	Thr Thr Ala Leu Lys	Thr Thr Thr Thr Ala	Leu Lys Thr

-continued

---

10475	10480	10485
Thr Ser Arg Ala Thr Leu Thr	Thr Ser Val Tyr Thr	Pro Thr Leu
10490	10495	10500
Gly Thr Leu Thr Pro Leu Asn	Ala Ser Met Gln Met	Ala Ser Thr
10505	10510	10515
Ile Pro Thr Glu Met Met Ile	Thr Thr Pro Tyr Val	Phe Pro Asp
10520	10525	10530
Val Pro Glu Thr Thr Ser Ser	Leu Ala Thr Ser Leu	Gly Ala Glu
10535	10540	10545
Thr Ser Thr Ala Leu Pro Arg	Thr Thr Pro Ser Val	Phe Asn Arg
10550	10555	10560
Glu Ser Glu Thr Thr Ala Ser	Leu Val Ser Arg Ser	Gly Ala Glu
10565	10570	10575
Arg Ser Pro Val Ile Gln Thr	Leu Asp Val Ser Ser	Ser Glu Pro
10580	10585	10590
Asp Thr Thr Ala Ser Trp Val	Ile His Pro Ala Glu	Thr Ile Pro
10595	10600	10605
Thr Val Ser Lys Thr Thr Pro	Asn Phe Phe His Ser	Glu Leu Asp
10610	10615	10620
Thr Val Ser Ser Thr Ala Thr	Ser His Gly Ala Asp	Val Ser Ser
10625	10630	10635
Ala Ile Pro Thr Asn Ile Ser	Pro Ser Glu Leu Asp	Ala Leu Thr
10640	10645	10650
Pro Leu Val Thr Ile Ser Gly	Thr Asp Thr Ser Thr	Thr Phe Pro
10655	10660	10665
Thr Leu Thr Lys Ser Pro His	Glu Thr Glu Thr Arg	Thr Thr Trp
10670	10675	10680
Leu Thr His Pro Ala Glu Thr	Ser Ser Thr Ile Pro	Arg Thr Ile
10685	10690	10695
Pro Asn Phe Ser His His Glu	Ser Asp Ala Thr Pro	Ser Ile Ala
10700	10705	10710
Thr Ser Pro Gly Ala Glu Thr	Ser Ser Ala Ile Pro	Ile Met Thr
10715	10720	10725
Val Ser Pro Gly Ala Glu Asp	Leu Val Thr Ser Gln	Val Thr Ser
10730	10735	10740
Ser Gly Thr Asp Arg Asn Met	Thr Ile Pro Thr Leu	Thr Leu Ser
10745	10750	10755
Pro Gly Glu Pro Lys Thr Ile	Ala Ser Leu Val Thr	His Pro Glu
10760	10765	10770
Ala Gln Thr Ser Ser Ala Ile	Pro Thr Ser Thr Ile	Ser Pro Ala
10775	10780	10785
Val Ser Arg Leu Val Thr Ser	Met Val Thr Ser Leu	Ala Ala Lys
10790	10795	10800
Thr Ser Thr Thr Asn Arg Ala	Leu Thr Asn Ser Pro	Gly Glu Pro
10805	10810	10815
Ala Thr Thr Val Ser Leu Val	Thr His Pro Ala Gln	Thr Ser Pro
10820	10825	10830
Thr Val Pro Trp Thr Thr Ser	Ile Phe Phe His Ser	Lys Ser Asp
10835	10840	10845
Thr Thr Pro Ser Met Thr Thr	Ser His Gly Ala Glu	Ser Ser Ser
10850	10855	10860
Ala Val Pro Thr Pro Thr Val	Ser Thr Glu Val Pro	Gly Val Val
10865	10870	10875

-continued

---

Thr Pro 10880	Leu Val Thr Ser Ser 10885	Arg Ala Val Ile Ser 10890	Thr Thr Ile
Pro Ile 10895	Leu Thr Leu Ser Pro 10900	Gly Glu Pro Glu Thr 10905	Thr Pro Ser
Met Ala 10910	Thr Ser His Gly Glu 10915	Glu Ala Ser Ser Ala 10920	Ile Pro Thr
Pro Thr 10925	Val Ser Pro Gly Val 10930	Pro Gly Val Val Thr 10935	Ser Leu Val
Thr Ser 10940	Ser Arg Ala Val Thr 10945	Ser Thr Thr Ile Pro 10950	Ile Leu Thr
Phe Ser 10955	Leu Gly Glu Pro Glu 10960	Thr Thr Pro Ser Met 10965	Ala Thr Ser
His Gly 10970	Thr Glu Ala Gly Ser 10975	Ala Val Pro Thr Val 10980	Leu Pro Glu
Val Pro 10985	Gly Met Val Thr Ser 10990	Leu Val Ala Ser Ser 10995	Arg Ala Val
Thr Ser 11000	Thr Thr Leu Pro Thr 11005	Leu Thr Leu Ser Pro 11010	Gly Glu Pro
Glu Thr 11015	Thr Pro Ser Met Ala 11020	Thr Ser His Gly Ala 11025	Glu Ala Ser
Ser Thr 11030	Val Pro Thr Val Ser 11035	Pro Glu Val Pro Gly 11040	Val Val Thr
Ser Leu 11045	Val Thr Ser Ser Ser 11050	Gly Val Asn Ser Thr 11055	Ser Ile Pro
Thr Leu 11060	Ile Leu Ser Pro Gly 11065	Glu Leu Glu Thr Thr 11070	Pro Ser Met
Ala Thr 11075	Ser His Gly Ala Glu 11080	Ala Ser Ser Ala Val 11085	Pro Thr Pro
Thr Val 11090	Ser Pro Gly Val Ser 11095	Gly Val Val Thr Pro 11100	Leu Val Thr
Ser Ser 11105	Arg Ala Val Thr Ser 11110	Thr Thr Ile Pro Ile 11115	Leu Thr Leu
Ser Ser 11120	Ser Glu Pro Glu Thr 11125	Thr Pro Ser Met Ala 11130	Thr Ser His
Gly Val 11135	Glu Ala Ser Ser Ala 11140	Val Leu Thr Val Ser 11145	Pro Glu Val
Pro Gly 11150	Met Val Thr Ser Leu 11155	Val Thr Ser Ser Arg 11160	Ala Val Thr
Ser Thr 11165	Thr Ile Pro Thr Leu 11170	Thr Ile Ser Ser Asp 11175	Glu Pro Glu
Thr Thr 11180	Thr Ser Leu Val Thr 11185	His Ser Glu Ala Lys 11190	Met Ile Ser
Ala Ile 11195	Pro Thr Leu Ala Val 11200	Ser Pro Thr Val Gln 11205	Gly Leu Val
Thr Ser 11210	Leu Val Thr Ser Ser 11215	Gly Ser Glu Thr Ser 11220	Ala Phe Ser
Asn Leu 11225	Thr Val Ala Ser Ser 11230	Gln Pro Glu Thr Ile 11235	Asp Ser Trp
Val Ala 11240	His Pro Gly Thr Glu 11245	Ala Ser Ser Val Val 11250	Pro Thr Leu
Thr Val 11255	Ser Thr Gly Glu Pro 11260	Phe Thr Asn Ile Ser 11265	Leu Val Thr



-continued

His 11270	Pro 11270	Ala 11270	Glu 11270	Ser 11270	Ser 11270	Ser 11275	Thr 11275	Leu 11275	Pro 11275	Arg 11275	Thr 11280	Thr 11280	Ser 11280	Arg 11280
Phe 11285	Ser 11285	His 11285	Ser 11285	Glu 11285	Leu 11285	Asp 11290	Thr 11290	Met 11290	Pro 11290	Ser 11290	Thr 11295	Val 11295	Thr 11295	Ser 11295
Pro 11300	Glu 11300	Ala 11300	Glu 11300	Ser 11300	Ser 11300	Ser 11305	Ala 11305	Ile 11305	Ser 11305	Thr 11305	Thr 11310	Ile 11310	Ser 11310	Pro 11310
Gly 11315	Ile 11315	Pro 11315	Gly 11315	Val 11315	Leu 11315	Thr 11320	Ser 11320	Leu 11320	Val 11320	Thr 11320	Ser 11325	Ser 11325	Gly 11325	Arg 11325
Asp 11330	Ile 11330	Ser 11330	Ala 11330	Thr 11330	Phe 11330	Pro 11335	Thr 11335	Val 11335	Pro 11335	Glu 11335	Ser 11340	Pro 11340	His 11340	Glu 11340
Ser 11345	Glu 11345	Ala 11345	Thr 11345	Ala 11345	Ser 11345	Trp 11350	Val 11350	Thr 11350	His 11350	Pro 11350	Ala 11355	Val 11355	Thr 11355	Ser 11355
Thr 11360	Thr 11360	Val 11360	Pro 11360	Arg 11360	Thr 11360	Thr 11365	Pro 11365	Asn 11365	Tyr 11365	Ser 11365	His 11370	Ser 11370	Glu 11370	Pro 11370
Asp 11375	Thr 11375	Thr 11375	Pro 11375	Ser 11375	Ile 11375	Ala 11380	Thr 11380	Ser 11380	Pro 11380	Gly 11380	Ala 11385	Glu 11385	Ala 11385	Thr 11385
Ser 11390	Asp 11390	Phe 11390	Pro 11390	Thr 11390	Ile 11390	Thr 11395	Val 11395	Ser 11395	Pro 11395	Asp 11395	Val 11400	Pro 11400	Asp 11400	Met 11400
Val 11405	Thr 11405	Ser 11405	Gln 11405	Val 11405	Thr 11405	Ser 11410	Ser 11410	Gly 11410	Thr 11410	Asp 11410	Thr 11415	Ser 11415	Ile 11415	Thr 11415
Ile 11420	Pro 11420	Thr 11420	Leu 11420	Thr 11420	Leu 11420	Ser 11425	Ser 11425	Gly 11425	Glu 11425	Pro 11425	Glu 11430	Thr 11430	Thr 11430	Thr 11430
Ser 11435	Phe 11435	Ile 11435	Thr 11435	Tyr 11435	Ser 11435	Glu 11440	Thr 11440	His 11440	Thr 11440	Ser 11440	Ser 11445	Ala 11445	Ile 11445	Pro 11445
Thr 11450	Leu 11450	Pro 11450	Val 11450	Ser 11450	Pro 11450	Gly 11455	Ala 11455	Ser 11455	Lys 11455	Met 11455	Leu 11460	Thr 11460	Ser 11460	Leu 11460
Val 11465	Ile 11465	Ser 11465	Ser 11465	Gly 11465	Thr 11465	Asp 11470	Ser 11470	Thr 11470	Thr 11470	Thr 11470	Phe 11475	Pro 11475	Thr 11475	Leu 11475
Thr 11480	Glu 11480	Thr 11480	Pro 11480	Tyr 11480	Glu 11480	Pro 11485	Glu 11485	Thr 11485	Thr 11485	Ala 11485	Ile 11490	Gln 11490	Leu 11490	Ile 11490
His 11495	Pro 11495	Ala 11495	Glu 11495	Thr 11495	Asn 11495	Thr 11500	Met 11500	Val 11500	Pro 11500	Arg 11500	Thr 11505	Thr 11505	Pro 11505	Lys 11505
Phe 11510	Ser 11510	His 11510	Ser 11510	Lys 11510	Ser 11510	Asp 11515	Thr 11515	Thr 11515	Leu 11515	Pro 11515	Val 11520	Ala 11520	Ile 11520	Thr 11520
Ser 11525	Pro 11525	Gly 11525	Pro 11525	Glu 11525	Ala 11525	Ser 11530	Ser 11530	Ala 11530	Val 11530	Ser 11530	Thr 11535	Thr 11535	Thr 11535	Ile 11535
Ser 11540	Pro 11540	Asp 11540	Met 11540	Ser 11540	Asp 11540	Leu 11545	Val 11545	Thr 11545	Ser 11545	Leu 11545	Val 11550	Pro 11550	Ser 11550	Ser 11550
Gly 11555	Thr 11555	Asp 11555	Thr 11555	Ser 11555	Thr 11555	Thr 11560	Phe 11560	Pro 11560	Thr 11560	Leu 11560	Ser 11565	Glu 11565	Thr 11565	Pro 11565
Tyr 11570	Glu 11570	Pro 11570	Glu 11570	Thr 11570	Thr 11570	Ala 11575	Thr 11575	Trp 11575	Leu 11575	Thr 11575	His 11580	Pro 11580	Ala 11580	Glu 11580
Thr 11585	Ser 11585	Thr 11585	Thr 11585	Val 11585	Ser 11585	Gly 11590	Thr 11590	Ile 11590	Pro 11590	Asn 11590	Phe 11595	Ser 11595	His 11595	Arg 11595
Gly 11600	Ser 11600	Asp 11600	Thr 11600	Ala 11600	Pro 11600	Ser 11605	Met 11605	Val 11605	Thr 11605	Ser 11605	Pro 11610	Gly 11610	Val 11610	Asp 11610
Thr 11615	Arg 11615	Ser 11615	Gly 11615	Val 11615	Pro 11615	Thr 11620	Thr 11620	Thr 11620	Ile 11620	Pro 11620	Pro 11625	Ser 11625	Ile 11625	Pro 11625
Gly 11630	Val 11630	Val 11630	Thr 11630	Ser 11630	Gln 11630	Val 11635	Thr 11635	Ser 11635	Ser 11635	Ala 11635	Thr 11640	Asp 11640	Thr 11640	Ser 11640
Thr 11645	Ala 11645	Ile 11645	Pro 11645	Thr 11645	Leu 11645	Thr 11650	Pro 11650	Ser 11650	Pro 11650	Gly 11650	Glu 11655	Pro 11655	Glu 11655	Thr 11655
Thr 11655	Ala 11655	Ser 11655	Ser 11655	Ala 11655	Thr 11655	His 11655	Pro 11655	Gly 11655	Thr 11655	Gln 11655	Thr 11655	Gly 11655	Phe 11655	Thr 11655

-continued

---

11660					11665						11670				
Val Pro	Ile Arg Thr	Val Pro	Ser Ser Glu Pro Asp	Thr Met Ala											
11675					11680						11685				
Ser Trp	Val Thr His Pro	Pro	Gln Thr Ser Thr Pro	Val Ser Arg											
11690					11695						11700				
Thr Thr	Ser Ser Phe Ser	His	Ser Ser Pro Asp Ala	Thr Pro Val											
11705					11710						11715				
Met Ala	Thr Ser Pro Arg	Thr	Glu Ala Ser Ser Ala	Val Leu Thr											
11720					11725						11730				
Thr Ile	Ser Pro Gly Ala	Pro	Glu Met Val Thr Ser	Gln Ile Thr											
11735					11740						11745				
Ser Ser	Gly Ala Ala Thr	Ser	Thr Thr Val Pro Thr	Leu Thr His											
11750					11755						11760				
Ser Pro	Gly Met Pro Glu	Thr	Thr Ala Leu Leu Ser	Thr His Pro											
11765					11770						11775				
Arg Thr	Glu Thr Ser Lys	Thr	Phe Pro Ala Ser Thr	Val Phe Pro											
11780					11785						11790				
Gln Val	Ser Glu Thr Thr	Ala	Ser Leu Thr Ile Arg	Pro Gly Ala											
11795					11800						11805				
Glu Thr	Ser Thr Ala Leu	Pro	Thr Gln Thr Thr Ser	Ser Leu Phe											
11810					11815						11820				
Thr Leu	Leu Val Thr Gly	Thr	Ser Arg Val Asp Leu	Ser Pro Thr											
11825					11830						11835				
Ala Ser	Pro Gly Val Ser	Ala	Lys Thr Ala Pro Leu	Ser Thr His											
11840					11845						11850				
Pro Gly	Thr Glu Thr Ser	Thr	Met Ile Pro Thr Ser	Thr Leu Ser											
11855					11860						11865				
Leu Gly	Leu Leu Glu Thr	Thr	Gly Leu Leu Ala Thr	Ser Ser Ser											
11870					11875						11880				
Ala Glu	Thr Ser Thr Ser	Thr	Leu Thr Leu Thr Val	Ser Pro Ala											
11885					11890						11895				
Val Ser	Gly Leu Ser Ser	Ala	Ser Ile Thr Thr Asp	Lys Pro Gln											
11900					11905						11910				
Thr Val	Thr Ser Trp Asn	Thr	Glu Thr Ser Pro Ser	Val Thr Ser											
11915					11920						11925				
Val Gly	Pro Pro Glu Phe	Ser	Arg Thr Val Thr Gly	Thr Thr Met											
11930					11935						11940				
Thr Leu	Ile Pro Ser Glu	Met	Pro Thr Pro Pro Lys	Thr Ser His											
11945					11950						11955				
Gly Glu	Gly Val Ser Pro	Thr	Thr Ile Leu Arg Thr	Thr Met Val											
11960					11965						11970				
Glu Ala	Thr Asn Leu Ala	Thr	Thr Gly Ser Ser Pro	Thr Val Ala											
11975					11980						11985				
Lys Thr	Thr Thr Thr Phe	Asn	Thr Leu Ala Gly Ser	Leu Phe Thr											
11990					11995						12000				
Pro Leu	Thr Thr Pro Gly	Met	Ser Thr Leu Ala Ser	Glu Ser Val											
12005					12010						12015				
Thr Ser	Arg Thr Ser Tyr	Asn	His Arg Ser Trp Ile	Ser Thr Thr											
12020					12025						12030				
Ser Ser	Tyr Asn Arg Arg	Tyr	Trp Thr Pro Ala Thr	Ser Thr Pro											
12035					12040						12045				
Val Thr	Ser Thr Phe Ser	Pro	Gly Ile Ser Thr Ser	Ser Ile Pro											
12050					12055						12060				

-continued

---

Ser	Ser	Thr	Ala	Ala	Thr	Val	Pro	Phe	Met	Val	Pro	Phe	Thr	Leu
12065						12070					12075			
Asn	Phe	Thr	Ile	Thr	Asn	Leu	Gln	Tyr	Glu	Glu	Asp	Met	Arg	His
12080						12085					12090			
Pro	Gly	Ser	Arg	Lys	Phe	Asn	Ala	Thr	Glu	Arg	Glu	Leu	Gln	Gly
12095						12100					12105			
Leu	Leu	Lys	Pro	Leu	Phe	Arg	Asn	Ser	Ser	Leu	Glu	Tyr	Leu	Tyr
12110						12115					12120			
Ser	Gly	Cys	Arg	Leu	Ala	Ser	Leu	Arg	Pro	Glu	Lys	Asp	Ser	Ser
12125						12130					12135			
Ala	Thr	Ala	Val	Asp	Ala	Ile	Cys	Thr	His	Arg	Pro	Asp	Pro	Glu
12140						12145					12150			
Asp	Leu	Gly	Leu	Asp	Arg	Glu	Arg	Leu	Tyr	Trp	Glu	Leu	Ser	Asn
12155						12160					12165			
Leu	Thr	Asn	Gly	Ile	Gln	Glu	Leu	Gly	Pro	Tyr	Thr	Leu	Asp	Arg
12170						12175					12180			
Asn	Ser	Leu	Tyr	Val	Asn	Gly	Phe	Thr	His	Arg	Ser	Ser	Met	Pro
12185						12190					12195			
Thr	Thr	Ser	Thr	Pro	Gly	Thr	Ser	Thr	Val	Asp	Val	Gly	Thr	Ser
12200						12205					12210			
Gly	Thr	Pro	Ser	Ser	Ser	Pro	Ser	Pro	Thr	Thr	Ala	Gly	Pro	Leu
12215						12220					12225			
Leu	Met	Pro	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Gln	Tyr
12230						12235					12240			
Glu	Glu	Asp	Met	Arg	Arg	Thr	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Met
12245						12250					12255			
Glu	Ser	Val	Leu	Gln	Gly	Leu	Leu	Lys	Pro	Leu	Phe	Lys	Asn	Thr
12260						12265					12270			
Ser	Val	Gly	Pro	Leu	Tyr	Ser	Gly	Cys	Arg	Leu	Thr	Leu	Leu	Arg
12275						12280					12285			
Pro	Glu	Lys	Asp	Gly	Ala	Ala	Thr	Gly	Val	Asp	Ala	Ile	Cys	Thr
12290						12295					12300			
His	Arg	Leu	Asp	Pro	Lys	Ser	Pro	Gly	Leu	Asn	Arg	Glu	Gln	Leu
12305						12310					12315			
Tyr	Trp	Glu	Leu	Ser	Lys	Leu	Thr	Asn	Asp	Ile	Glu	Glu	Leu	Gly
12320						12325					12330			
Pro	Tyr	Thr	Leu	Asp	Arg	Asn	Ser	Leu	Tyr	Val	Asn	Gly	Phe	Thr
12335						12340					12345			
His	Gln	Ser	Ser	Val	Ser	Thr	Thr	Ser	Thr	Pro	Gly	Thr	Ser	Thr
12350						12355					12360			
Val	Asp	Leu	Arg	Thr	Ser	Gly	Thr	Pro	Ser	Ser	Leu	Ser	Ser	Pro
12365						12370					12375			
Thr	Ile	Met	Ala	Ala	Gly	Pro	Leu	Leu	Val	Pro	Phe	Thr	Leu	Asn
12380						12385					12390			
Phe	Thr	Ile	Thr	Asn	Leu	Gln	Tyr	Gly	Glu	Asp	Met	Gly	His	Pro
12395						12400					12405			
Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr	Glu	Arg	Val	Leu	Gln	Gly	Leu
12410						12415					12420			
Leu	Gly	Pro	Ile	Phe	Lys	Asn	Thr	Ser	Val	Gly	Pro	Leu	Tyr	Ser
12425						12430					12435			
Gly	Cys	Arg	Leu	Thr	Ser	Leu	Arg	Ser	Glu	Lys	Asp	Gly	Ala	Ala
12440						12445					12450			

-continued

Thr Gly 12455	Val Asp Ala Ile Cys 12460	Ile His His Leu Asp 12465	Pro Lys Ser
Pro Gly 12470	Leu Asn Arg Glu Arg 12475	Leu Tyr Trp Glu Leu 12480	Ser Gln Leu
Thr Asn 12485	Gly Ile Lys Glu Leu 12490	Gly Pro Tyr Thr Leu 12495	Asp Arg Asn
Ser Leu 12500	Tyr Val Asn Gly Phe 12505	Thr His Arg Thr Ser 12510	Val Pro Thr
Ser Ser 12515	Thr Pro Gly Thr Ser 12520	Thr Val Asp Leu Gly 12525	Thr Ser Gly
Thr Pro 12530	Phe Ser Leu Pro Ser 12535	Pro Ala Thr Ala Gly 12540	Pro Leu Leu
Val Leu 12545	Phe Thr Leu Asn Phe 12550	Thr Ile Thr Asn Leu 12555	Lys Tyr Glu
Glu Asp 12560	Met His Arg Pro Gly 12565	Ser Arg Lys Phe Asn 12570	Thr Thr Glu
Arg Val 12575	Leu Gln Thr Leu Leu 12580	Gly Pro Met Phe Lys 12585	Asn Thr Ser
Val Gly 12590	Leu Leu Tyr Ser Gly 12595	Cys Arg Leu Thr Leu 12600	Leu Arg Ser
Glu Lys 12605	Asp Gly Ala Ala Thr 12610	Gly Val Asp Ala Ile 12615	Cys Thr His
Arg Leu 12620	Asp Pro Lys Ser Pro 12625	Gly Val Asp Arg Glu 12630	Gln Leu Tyr
Trp Glu 12635	Leu Ser Gln Leu Thr 12640	Asn Gly Ile Lys Glu 12645	Leu Gly Pro
Tyr Thr 12650	Leu Asp Arg Asn Ser 12655	Leu Tyr Val Asn Gly 12660	Phe Thr His
Trp Ile 12665	Pro Val Pro Thr Ser 12670	Ser Thr Pro Gly Thr 12675	Ser Thr Val
Asp Leu 12680	Gly Ser Gly Thr Pro 12685	Ser Ser Leu Pro Ser 12690	Pro Thr Thr
Ala Gly 12695	Pro Leu Leu Val Pro 12700	Phe Thr Leu Asn Phe 12705	Thr Ile Thr
Asn Leu 12710	Lys Tyr Glu Glu Asp 12715	Met His Cys Pro Gly 12720	Ser Arg Lys
Phe Asn 12725	Thr Thr Glu Arg Val 12730	Leu Gln Ser Leu Leu 12735	Gly Pro Met
Phe Lys 12740	Asn Thr Ser Val Gly 12745	Pro Leu Tyr Ser Gly 12750	Cys Arg Leu
Thr Leu 12755	Leu Arg Ser Glu Lys 12760	Asp Gly Ala Ala Thr 12765	Gly Val Asp
Ala Ile 12770	Cys Thr His Arg Leu 12775	Asp Pro Lys Ser Pro 12780	Gly Val Asp
Arg Glu 12785	Gln Leu Tyr Trp Glu 12790	Leu Ser Gln Leu Thr 12795	Asn Gly Ile
Lys Glu 12800	Leu Gly Pro Tyr Thr 12805	Leu Asp Arg Asn Ser 12810	Leu Tyr Val
Asn Gly 12815	Phe Thr His Gln Thr 12820	Ser Ala Pro Asn Thr 12825	Ser Thr Pro
Gly Thr 12830	Ser Thr Val Asp Leu 12835	Gly Thr Ser Gly Thr 12840	Pro Ser Ser
Leu Pro	Ser Pro Thr Ser Ala	Gly Pro Leu Leu Val	Pro Phe Thr

-continued

12845	12850	12855
Leu Asn Phe Thr Ile Thr Asn	Leu Gln Tyr Glu Glu	Asp Met His
12860	12865	12870
His Pro Gly Ser Arg Lys Phe	Asn Thr Thr Glu Arg	Val Leu Gln
12875	12880	12885
Gly Leu Leu Gly Pro Met Phe	Lys Asn Thr Ser Val	Gly Leu Leu
12890	12895	12900
Tyr Ser Gly Cys Arg Leu Thr	Leu Leu Arg Pro Glu	Lys Asn Gly
12905	12910	12915
Ala Ala Thr Gly Met Asp Ala	Ile Cys Ser His Arg	Leu Asp Pro
12920	12925	12930
Lys Ser Pro Gly Leu Asn Arg	Glu Gln Leu Tyr Trp	Glu Leu Ser
12935	12940	12945
Gln Leu Thr His Gly Ile Lys	Glu Leu Gly Pro Tyr	Thr Leu Asp
12950	12955	12960
Arg Asn Ser Leu Tyr Val Asn	Gly Phe Thr His Arg	Ser Ser Val
12965	12970	12975
Ala Pro Thr Ser Thr Pro Gly	Thr Ser Thr Val Asp	Leu Gly Thr
12980	12985	12990
Ser Gly Thr Pro Ser Ser Leu	Pro Ser Pro Thr Thr	Ala Val Pro
12995	13000	13005
Leu Leu Val Pro Phe Thr Leu	Asn Phe Thr Ile Thr	Asn Leu Gln
13010	13015	13020
Tyr Gly Glu Asp Met Arg His	Pro Gly Ser Arg Lys	Phe Asn Thr
13025	13030	13035
Thr Glu Arg Val Leu Gln Gly	Leu Leu Gly Pro Leu	Phe Lys Asn
13040	13045	13050
Ser Ser Val Gly Pro Leu Tyr	Ser Gly Cys Arg Leu	Ile Ser Leu
13055	13060	13065
Arg Ser Glu Lys Asp Gly Ala	Ala Thr Gly Val Asp	Ala Ile Cys
13070	13075	13080
Thr His His Leu Asn Pro Gln	Ser Pro Gly Leu Asp	Arg Glu Gln
13085	13090	13095
Leu Tyr Trp Gln Leu Ser Gln	Met Thr Asn Gly Ile	Lys Glu Leu
13100	13105	13110
Gly Pro Tyr Thr Leu Asp Arg	Asn Ser Leu Tyr Val	Asn Gly Phe
13115	13120	13125
Thr His Arg Ser Ser Gly Leu	Thr Thr Ser Thr Pro	Trp Thr Ser
13130	13135	13140
Thr Val Asp Leu Gly Thr Ser	Gly Thr Pro Ser Pro	Val Pro Ser
13145	13150	13155
Pro Thr Thr Thr Gly Pro Leu	Leu Val Pro Phe Thr	Leu Asn Phe
13160	13165	13170
Thr Ile Thr Asn Leu Gln Tyr	Glu Glu Asn Met Gly	His Pro Gly
13175	13180	13185
Ser Arg Lys Phe Asn Ile Thr	Glu Ser Val Leu Gln	Gly Leu Leu
13190	13195	13200
Lys Pro Leu Phe Lys Ser Thr	Ser Val Gly Pro Leu	Tyr Ser Gly
13205	13210	13215
Cys Arg Leu Thr Leu Leu Arg	Pro Glu Lys Asp Gly	Val Ala Thr
13220	13225	13230
Arg Val Asp Ala Ile Cys Thr	His Arg Pro Asp Pro	Lys Ile Pro
13235	13240	13245

-continued

Gly Leu 13250	Asp Arg Gln Gln Leu 13255	Tyr Trp Glu Leu Ser 13260	Gln Leu Thr
His Ser 13265	Ile Thr Glu Leu Gly 13270	Pro Tyr Thr Leu Asp 13275	Arg Asp Ser
Leu Tyr 13280	Val Asn Gly Phe Thr 13285	Gln Arg Ser Ser Val 13290	Pro Thr Thr
Ser Thr 13295	Pro Gly Thr Phe Thr 13300	Val Gln Pro Glu Thr 13305	Ser Glu Thr
Pro Ser 13310	Ser Leu Pro Gly Pro 13315	Thr Ala Thr Gly Pro 13320	Val Leu Leu
Pro Phe 13325	Thr Leu Asn Phe Thr 13330	Ile Thr Asn Leu Gln 13335	Tyr Glu Glu
Asp Met 13340	Arg Arg Pro Gly Ser 13345	Arg Lys Phe Asn Thr 13350	Thr Glu Arg
Val Leu 13355	Gln Gly Leu Leu Met 13360	Pro Leu Phe Lys Asn 13365	Thr Ser Val
Ser Ser 13370	Leu Tyr Ser Gly Cys 13375	Arg Leu Thr Leu Leu 13380	Arg Pro Glu
Lys Asp 13385	Gly Ala Ala Thr Arg 13390	Val Asp Ala Val Cys 13395	Thr His Arg
Pro Asp 13400	Pro Lys Ser Pro Gly 13405	Leu Asp Arg Glu Arg 13410	Leu Tyr Trp
Lys Leu 13415	Ser Gln Leu Thr His 13420	Gly Ile Thr Glu Leu 13425	Gly Pro Tyr
Thr Leu 13430	Asp Arg His Ser Leu 13435	Tyr Val Asn Gly Phe 13440	Thr His Gln
Ser Ser 13445	Met Thr Thr Thr Arg 13450	Thr Pro Asp Thr Ser 13455	Thr Met His
Leu Ala 13460	Thr Ser Arg Thr Pro 13465	Ala Ser Leu Ser Gly 13470	Pro Met Thr
Ala Ser 13475	Pro Leu Leu Val Leu 13480	Phe Thr Ile Asn Phe 13485	Thr Ile Thr
Asn Leu 13490	Arg Tyr Glu Glu Asn 13495	Met His His Pro Gly 13500	Ser Arg Lys
Phe Asn 13505	Thr Thr Glu Arg Val 13510	Leu Gln Gly Leu Leu 13515	Arg Pro Val
Phe Lys 13520	Asn Thr Ser Val Gly 13525	Pro Leu Tyr Ser Gly 13530	Cys Arg Leu
Thr Leu 13535	Leu Arg Pro Lys Lys 13540	Asp Gly Ala Ala Thr 13545	Lys Val Asp
Ala Ile 13550	Cys Thr Tyr Arg Pro 13555	Asp Pro Lys Ser Pro 13560	Gly Leu Asp
Arg Glu 13565	Gln Leu Tyr Trp Glu 13570	Leu Ser Gln Leu Thr 13575	His Ser Ile
Thr Glu 13580	Leu Gly Pro Tyr Thr 13585	Leu Asp Arg Asp Ser 13590	Leu Tyr Val
Asn Gly 13595	Phe Thr Gln Arg Ser 13600	Ser Val Pro Thr Thr 13605	Ser Ile Pro
Gly Thr 13610	Pro Thr Val Asp Leu 13615	Gly Thr Ser Gly Thr 13620	Pro Val Ser
Lys Pro 13625	Gly Pro Ser Ala Ala 13630	Ser Pro Leu Leu Val 13635	Leu Phe Thr

-continued

Leu Asn 13640	Phe Thr Ile Thr	Asn	Leu Arg Tyr Glu Glu	Asn Met Gln 13650
His Pro 13655	Gly Ser Arg Lys Phe	Asn Thr Thr Glu Arg	Val Leu Gln 13665	
Gly Leu 13670	Leu Arg Ser Leu Phe	Lys Ser Thr Ser Val	Gly Pro Leu 13680	
Tyr Ser 13685	Gly Cys Arg Leu Thr	Leu Leu Arg Pro Glu	Lys Asp Gly 13695	
Thr Ala 13700	Thr Gly Val Asp Ala	Ile Cys Thr His His	Pro Asp Pro 13710	
Lys Ser 13715	Pro Arg Leu Asp Arg	Glu Gln Leu Tyr Trp	Glu Leu Ser 13725	
Gln Leu 13730	Thr His Asn Ile Thr	Glu Leu Gly Pro Tyr	Ala Leu Asp 13740	
Asn Asp 13745	Ser Leu Phe Val Asn	Gly Phe Thr His Arg	Ser Ser Val 13755	
Ser Thr 13760	Thr Ser Thr Pro Gly	Thr Pro Thr Val Tyr	Leu Gly Ala 13770	
Ser Lys 13775	Thr Pro Ala Ser Ile	Phe Gly Pro Ser Ala	Ala Ser His 13785	
Leu Leu 13790	Ile Leu Phe Thr Leu	Asn Phe Thr Ile Thr	Asn Leu Arg 13800	
Tyr Glu 13805	Glu Asn Met Trp Pro	Gly Ser Arg Lys Phe	Asn Thr Thr 13815	
Glu Arg 13820	Val Leu Gln Gly Leu	Leu Arg Pro Leu Phe	Lys Asn Thr 13830	
Ser Val 13835	Gly Pro Leu Tyr Ser	Gly Cys Arg Leu Thr	Leu Leu Arg 13845	
Pro Glu 13850	Lys Asp Gly Glu Ala	Thr Gly Val Asp Ala	Ile Cys Thr 13860	
His Arg 13865	Pro Asp Pro Thr Gly	Pro Gly Leu Asp Arg	Glu Gln Leu 13875	
Tyr Leu 13880	Glu Leu Ser Gln Leu	Thr His Ser Ile Thr	Glu Leu Gly 13890	
Pro Tyr 13895	Thr Leu Asp Arg Asp	Ser Leu Tyr Val Asn	Gly Phe Thr 13905	
His Arg 13910	Ser Ser Val Pro Thr	Thr Ser Thr Gly Val	Val Ser Glu 13920	
Glu Pro 13925	Phe Thr Leu Asn Phe	Thr Ile Asn Asn Leu	Arg Tyr Met 13935	
Ala Asp 13940	Met Gly Gln Pro Gly	Ser Leu Lys Phe Asn	Ile Thr Asp 13950	
Asn Val 13955	Met Gln His Leu Leu	Ser Pro Leu Phe Gln	Arg Ser Ser 13965	
Leu Gly 13970	Ala Arg Tyr Thr Gly	Cys Arg Val Ile Ala	Leu Arg Ser 13980	
Val Lys 13985	Asn Gly Ala Glu Thr	Arg Val Asp Leu Leu	Cys Thr Tyr 13995	
Leu Gln 14000	Pro Leu Ser Gly Pro	Gly Leu Pro Ile Lys	Gln Val Phe 14010	
His Glu 14015	Leu Ser Gln Gln Thr	His Gly Ile Thr Arg	Leu Gly Pro 14025	
Tyr Ser	Leu Asp Lys Asp Ser	Leu Tyr Leu Asn Gly	Tyr Asn Glu	

-continued

---

14030		14035		14040
Pro Gly	Pro Asp Glu	Pro Pro	Thr Thr Pro Lys	Pro Ala Thr Thr
14045		14050		14055
Phe Leu	Pro Pro Leu Ser	Glu Ala Thr Thr	Ala Met	Gly Tyr His
14060		14065		14070
Leu Lys	Thr Leu Thr Leu	Asn Phe Thr Ile Ser	Asn	Leu Gln Tyr
14075		14080		14085
Ser Pro	Asp Met Gly Lys	Gly Ser Ala Thr Phe	Asn	Ser Thr Glu
14090		14095		14100
Gly Val	Leu Gln His Leu	Leu Arg Pro Leu Phe	Gln	Lys Ser Ser
14105		14110		14115
Met Gly	Pro Phe Tyr Leu	Gly Cys Gln Leu Ile	Ser	Leu Arg Pro
14120		14125		14130
Glu Lys	Asp Gly Ala Ala	Thr Gly Val Asp Thr	Thr	Cys Thr Tyr
14135		14140		14145
His Pro	Asp Pro Val Gly	Pro Gly Leu Asp Ile	Gln	Gln Leu Tyr
14150		14155		14160
Trp Glu	Leu Ser Gln Leu	Thr His Gly Val Thr	Gln	Leu Gly Phe
14165		14170		14175
Tyr Val	Leu Asp Arg Asp	Ser Leu Phe Ile Asn	Gly	Tyr Ala Pro
14180		14185		14190
Gln Asn	Leu Ser Ile Arg	Gly Glu Tyr Gln Ile	Asn	Phe His Ile
14195		14200		14205
Val Asn	Trp Asn Leu Ser	Asn Pro Asp Pro Thr	Ser	Ser Glu Tyr
14210		14215		14220
Ile Thr	Leu Leu Arg Asp	Ile Gln Asp Lys Val	Thr	Thr Leu Tyr
14225		14230		14235
Lys Gly	Ser Gln Leu His	Asp Thr Phe Arg Phe	Cys	Leu Val Thr
14240		14245		14250
Asn Leu	Thr Met Asp Ser	Val Leu Val Thr Val	Lys	Ala Leu Phe
14255		14260		14265
Ser Ser	Asn Leu Asp Pro	Ser Leu Val Glu Gln	Val	Phe Leu Asp
14270		14275		14280
Lys Thr	Leu Asn Ala Ser	Phe His Trp Leu Gly	Ser	Thr Tyr Gln
14285		14290		14295
Leu Val	Asp Ile His Val	Thr Glu Met Glu Ser	Ser	Val Tyr Gln
14300		14305		14310
Pro Thr	Ser Ser Ser Ser	Thr Gln His Phe Tyr	Leu	Asn Phe Thr
14315		14320		14325
Ile Thr	Asn Leu Pro Tyr	Ser Gln Asp Lys Ala	Gln	Pro Gly Thr
14330		14335		14340
Thr Asn	Tyr Gln Arg Asn	Lys Arg Asn Ile Glu	Asp	Ala Leu Asn
14345		14350		14355
Gln Leu	Phe Arg Asn Ser	Ser Ile Lys Ser Tyr	Phe	Ser Asp Cys
14360		14365		14370
Gln Val	Ser Thr Phe Arg	Ser Val Pro Asn Arg	His	His Thr Gly
14375		14380		14385
Val Asp	Ser Leu Cys Asn	Phe Ser Pro Leu Ala	Arg	Arg Val Asp
14390		14395		14400
Arg Val	Ala Ile Tyr Glu	Glu Phe Leu Arg Met	Thr	Arg Asn Gly
14405		14410		14415
Thr Gln	Leu Gln Asn Phe	Thr Leu Asp Arg Ser	Ser	Val Leu Val
14420		14425		14430



-continued

---

Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser  
 14435 14440 14445  
 Asp Leu Pro Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu  
 14450 14455 14460  
 Leu Gly Val Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr  
 14465 14470 14475  
 Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys  
 14480 14485 14490  
 Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln  
 14495 14500 14505

<210> SEQ ID NO 58  
 <211> LENGTH: 630  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro  
 1 5 10 15  
 Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln  
 20 25 30  
 Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu  
 35 40 45  
 Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg  
 50 55 60  
 Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu  
 65 70 75 80  
 Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu  
 85 90 95  
 Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro  
 100 105 110  
 Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro  
 115 120 125  
 Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile  
 130 135 140  
 Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln  
 145 150 155 160  
 Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu  
 165 170 175  
 Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu  
 180 185 190  
 Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu  
 195 200 205  
 Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg  
 210 215 220  
 Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp  
 225 230 235 240  
 Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly  
 245 250 255  
 Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg  
 260 265 270  
 Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile  
 275 280 285  
 Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser

-continued

290	295	300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys 305 310 315 320		
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met 325 330 335		
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu 340 345 350		
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val 355 360 365		
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile 370 375 380		
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu 385 390 395 400		
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu 405 410 415		
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln 420 425 430		
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr 435 440 445		
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser 450 455 460		
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln 465 470 475 480		
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn 485 490 495		
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro 500 505 510		
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu 515 520 525		
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val 530 535 540		
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala 545 550 555 560		
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln 565 570 575		
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn 580 585 590		
Gly Tyr Leu Val Leu Asp Leu Ser Met Gln Glu Ala Leu Ser Gly Thr 595 600 605		
Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu 610 615 620		
Leu Ala Ser Thr Leu Ala 625 630		

&lt;210&gt; SEQ ID NO 59

&lt;211&gt; LENGTH: 622

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 59

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro 1 5 10 15
--

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln 20 25 30
---

-continued

---

Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
		35					40					45			
Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg
	50					55					60				
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu
65					70					75					80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu
				85					90					95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
			100					105					110		
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro
		115					120					125			
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile
	130					135					140				
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
145					150					155					160
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
				165					170					175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
			180					185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
		195					200					205			
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
	210					215					220				
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp
225					230					235					240
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
				245					250					255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
			260					265					270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile
		275					280					285			
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser
	290					295					300				
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys
305					310					315					320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
				325					330					335	
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
			340					345					350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
		355					360					365			
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
	370					375					380				
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
385					390					395					400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp
				405					410					415	
Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr
			420					425					430		
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu
		435					440					445			
Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp



-continued

---

Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His  
 210 215 220  
 Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser  
 225 230 235 240  
 Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser  
 245 250 255  
 Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val  
 260 265 270  
 Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile  
 275 280 285  
 Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn  
 290 295 300  
  
 <210> SEQ ID NO 61  
 <211> LENGTH: 314  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens  
  
 <400> SEQUENCE: 61  
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala  
 1 5 10 15  
 Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu  
 20 25 30  
 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro  
 35 40 45  
 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu  
 50 55 60  
 Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu  
 65 70 75 80  
 Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His  
 85 90 95  
 Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp  
 100 105 110  
 Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu  
 115 120 125  
 Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu  
 130 135 140  
 Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly  
 145 150 155 160  
 Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg  
 165 170 175  
 Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr Ser His  
 180 185 190  
 Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala  
 195 200 205  
 Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser  
 210 215 220  
 Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His Ser His  
 225 230 235 240  
 Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu  
 245 250 255  
 His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu  
 260 265 270  
 Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp  
 275 280 285

-continued

Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His  
290 295 300

Glu Leu Asp Ser Ala Ser Ser Glu Val Asn  
305 310

<210> SEQ ID NO 62

<211> LENGTH: 287

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala  
1 5 10 15

Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Asn  
20 25 30

Ala Val Ser Ser Glu Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro  
35 40 45

Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu  
50 55 60

Asp Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp  
65 70 75 80

Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser  
85 90 95

His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp  
100 105 110

Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr  
115 120 125

Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser  
130 135 140

Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu  
145 150 155 160

Asp Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys  
165 170 175

Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser  
180 185 190

Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala  
195 200 205

Glu Thr His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn  
210 215 220

Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser  
225 230 235 240

Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp  
245 250 255

Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys  
260 265 270

Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn  
275 280 285

<210> SEQ ID NO 63

<211> LENGTH: 411

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu  
1 5 10 15

-continued

---

Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Leu Glu Leu Asn  
 20 25 30  
 Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met  
 35 40 45  
 Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val  
 50 55 60  
 Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly  
 65 70 75 80  
 Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe  
 85 90 95  
 Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp  
 100 105 110  
 Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp  
 115 120 125  
 Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg  
 130 135 140  
 Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu  
 145 150 155 160  
 Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe  
 165 170 175  
 Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp  
 180 185 190  
 Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro  
 195 200 205  
 Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser  
 210 215 220  
 Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln  
 225 230 235 240  
 Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro  
 245 250 255  
 Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu  
 260 265 270  
 Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val  
 275 280 285  
 Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr  
 290 295 300  
 Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr  
 305 310 315 320  
 Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr  
 325 330 335  
 Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val  
 340 345 350  
 Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Glu Glu Cys  
 355 360 365  
 Ser Ala Asp Ser Asp Leu Asn Phe Leu Ile Pro Val Ala Val Gly Val  
 370 375 380  
 Ala Leu Gly Phe Leu Ile Ile Val Val Phe Ile Ser Tyr Met Ile Gly  
 385 390 395 400  
 Arg Arg Lys Ser Arg Thr Gly Tyr Gln Ser Val  
 405 410

&lt;210&gt; SEQ ID NO 64

&lt;211&gt; LENGTH: 410

-continued

---

```

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu
1          5          10          15
Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Leu Glu Leu Asn
20          25          30
Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met
35          40          45
Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val
50          55          60
Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly
65          70          75          80
Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe
85          90          95
Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp
100         105         110
Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp
115         120         125
Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg
130         135         140
Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu
145         150         155         160
Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe
165         170         175
Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp
180         185         190
Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro
195         200         205
Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser
210         215         220
Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln
225         230         235         240
Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro
245         250         255
Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu
260         265         270
Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val
275         280         285
Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr
290         295         300
Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr
305         310         315         320
Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr
325         330         335
Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val
340         345         350
Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Asp Cys
355         360         365
Ser Ala Asp Asp Asp Asn Phe Leu Val Pro Ile Ala Val Gly Ala Ala
370         375         380
Leu Ala Gly Val Leu Ile Leu Val Leu Leu Ala Tyr Phe Ile Gly Leu
385         390         395         400

```



-continued

Lys His His His Ala Gly Tyr Glu Gln Phe  
 405 410

<210> SEQ ID NO 65

<211> LENGTH: 410

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Met Val Cys Phe Arg Leu Phe Pro Val Pro Gly Ser Gly Leu Val Leu  
 1 5 10 15

Val Cys Leu Val Leu Gly Ala Val Arg Ser Tyr Ala Leu Glu Leu Asn  
 20 25 30

Leu Thr Asp Ser Glu Asn Ala Thr Cys Leu Tyr Ala Lys Trp Gln Met  
 35 40 45

Asn Phe Thr Val Arg Tyr Glu Thr Thr Asn Lys Thr Tyr Lys Thr Val  
 50 55 60

Thr Ile Ser Asp His Gly Thr Val Thr Tyr Asn Gly Ser Ile Cys Gly  
 65 70 75 80

Asp Asp Gln Asn Gly Pro Lys Ile Ala Val Gln Phe Gly Pro Gly Phe  
 85 90 95

Ser Trp Ile Ala Asn Phe Thr Lys Ala Ala Ser Thr Tyr Ser Ile Asp  
 100 105 110

Ser Val Ser Phe Ser Tyr Asn Thr Gly Asp Asn Thr Thr Phe Pro Asp  
 115 120 125

Ala Glu Asp Lys Gly Ile Leu Thr Val Asp Glu Leu Leu Ala Ile Arg  
 130 135 140

Ile Pro Leu Asn Asp Leu Phe Arg Cys Asn Ser Leu Ser Thr Leu Glu  
 145 150 155 160

Lys Asn Asp Val Val Gln His Tyr Trp Asp Val Leu Val Gln Ala Phe  
 165 170 175

Val Gln Asn Gly Thr Val Ser Thr Asn Glu Phe Leu Cys Asp Lys Asp  
 180 185 190

Lys Thr Ser Thr Val Ala Pro Thr Ile His Thr Thr Val Pro Ser Pro  
 195 200 205

Thr Thr Thr Pro Thr Pro Lys Glu Lys Pro Glu Ala Gly Thr Tyr Ser  
 210 215 220

Val Asn Asn Gly Asn Asp Thr Cys Leu Leu Ala Thr Met Gly Leu Gln  
 225 230 235 240

Leu Asn Ile Thr Gln Asp Lys Val Ala Ser Val Ile Asn Ile Asn Pro  
 245 250 255

Asn Thr Thr His Ser Thr Gly Ser Cys Arg Ser His Thr Ala Leu Leu  
 260 265 270

Arg Leu Asn Ser Ser Thr Ile Lys Tyr Leu Asp Phe Val Phe Ala Val  
 275 280 285

Lys Asn Glu Asn Arg Phe Tyr Leu Lys Glu Val Asn Ile Ser Met Tyr  
 290 295 300

Leu Val Asn Gly Ser Val Phe Ser Ile Ala Asn Asn Asn Leu Ser Tyr  
 305 310 315 320

Trp Asp Ala Pro Leu Gly Ser Ser Tyr Met Cys Asn Lys Glu Gln Thr  
 325 330 335

Val Ser Val Ser Gly Ala Phe Gln Ile Asn Thr Phe Asp Leu Arg Val  
 340 345 350

Gln Pro Phe Asn Val Thr Gln Gly Lys Tyr Ser Thr Ala Gln Glu Cys

-continued

355	360	365	
Ser Leu Asp Asp Asp Thr Ile Leu Ile Pro Ile Ile Val Gly Ala Gly			
370	375	380	
Leu Ser Gly Leu Ile Ile Val Ile Val Ile Ala Tyr Val Ile Gly Arg			
385	390	395	400
Arg Lys Ser Tyr Ala Gly Tyr Gln Thr Leu			
	405	410	

<210> SEQ ID NO 66  
 <211> LENGTH: 262  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

1	5	10	15
Met Trp Phe Leu Val Leu Cys Leu Ala Leu Ser Leu Gly Gly Thr Gly			
1	5	10	15
Ala Ala Pro Pro Ile Gln Ser Arg Ile Val Gly Gly Trp Glu Cys Glu			
20	25	30	
Gln His Ser Gln Pro Trp Gln Ala Ala Leu Tyr His Phe Ser Thr Phe			
35	40	45	
Gln Cys Gly Gly Ile Leu Val His Arg Gln Trp Val Leu Thr Ala Ala			
50	55	60	
His Cys Ile Ser Asp Asn Tyr Gln Leu Trp Leu Gly Arg His Asn Leu			
65	70	75	80
Phe Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser Phe			
85	90	95	
Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn His Thr Arg Gln			
100	105	110	
Ala Asp Glu Asp Tyr Ser His Asp Leu Met Leu Leu Arg Leu Thr Glu			
115	120	125	
Pro Ala Asp Thr Ile Thr Asp Ala Val Lys Val Val Glu Leu Pro Thr			
130	135	140	
Glu Glu Pro Glu Val Gly Ser Thr Cys Leu Ala Ser Gly Trp Gly Ser			
145	150	155	160
Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp Leu Gln Cys Val Asp			
165	170	175	
Leu Lys Ile Leu Pro Asn Asp Glu Cys Lys Lys Ala His Val Gln Lys			
180	185	190	
Val Thr Asp Phe Met Leu Cys Val Gly His Leu Glu Gly Gly Lys Asp			
195	200	205	
Thr Cys Val Gly Asp Ser Gly Gly Pro Leu Met Cys Asp Gly Val Leu			
210	215	220	
Gln Gly Val Thr Ser Trp Gly Tyr Val Pro Cys Gly Thr Pro Asn Lys			
225	230	235	240
Pro Ser Val Ala Val Arg Val Leu Ser Tyr Val Lys Trp Ile Glu Asp			
245	250	255	
Thr Ile Ala Glu Asn Ser			
260			

<210> SEQ ID NO 67  
 <211> LENGTH: 860  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Met Gly Pro Trp Gly Trp Lys Leu Arg Trp Thr Val Ala Leu Leu Leu

-continued

1	5	10	15
Ala Ala Ala Gly Thr Ala Val Gly Asp Arg Cys Glu Arg Asn Glu Phe 20 25 30			
Gln Cys Gln Asp Gly Lys Cys Ile Ser Tyr Lys Trp Val Cys Asp Gly 35 40 45			
Ser Ala Glu Cys Gln Asp Gly Ser Asp Glu Ser Gln Glu Thr Cys Leu 50 55 60			
Ser Val Thr Cys Lys Ser Gly Asp Phe Ser Cys Gly Gly Arg Val Asn 65 70 75 80			
Arg Cys Ile Pro Gln Phe Trp Arg Cys Asp Gly Gln Val Asp Cys Asp 85 90 95			
Asn Gly Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp 100 105 110			
Glu Phe Arg Cys His Asp Gly Lys Cys Ile Ser Arg Gln Phe Val Cys 115 120 125			
Asp Ser Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala Ser Cys Pro 130 135 140			
Val Leu Thr Cys Gly Pro Ala Ser Phe Gln Cys Asn Ser Ser Thr Cys 145 150 155 160			
Ile Pro Gln Leu Trp Ala Cys Asp Asn Asp Pro Asp Cys Glu Asp Gly 165 170 175			
Ser Asp Glu Trp Pro Gln Arg Cys Arg Gly Leu Tyr Val Phe Gln Gly 180 185 190			
Asp Ser Ser Pro Cys Ser Ala Phe Glu Phe His Cys Leu Ser Gly Glu 195 200 205			
Cys Ile His Ser Ser Trp Arg Cys Asp Gly Gly Pro Asp Cys Lys Asp 210 215 220			
Lys Ser Asp Glu Glu Asn Cys Ala Val Ala Thr Cys Arg Pro Asp Glu 225 230 235 240			
Phe Gln Cys Ser Asp Gly Asn Cys Ile His Gly Ser Arg Gln Cys Asp 245 250 255			
Arg Glu Tyr Asp Cys Lys Asp Met Ser Asp Glu Val Gly Cys Val Asn 260 265 270			
Val Thr Leu Cys Glu Gly Pro Asn Lys Phe Lys Cys His Ser Gly Glu 275 280 285			
Cys Ile Thr Leu Asp Lys Val Cys Asn Met Ala Arg Asp Cys Arg Asp 290 295 300			
Trp Ser Asp Glu Pro Ile Lys Glu Cys Gly Thr Asn Glu Cys Leu Asp 305 310 315 320			
Asn Asn Gly Gly Cys Ser His Val Cys Asn Asp Leu Lys Ile Gly Tyr 325 330 335			
Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu Val Ala Gln Arg Arg Cys 340 345 350			
Glu Asp Ile Asp Glu Cys Gln Asp Pro Asp Thr Cys Ser Gln Leu Cys 355 360 365			
Val Asn Leu Glu Gly Gly Tyr Lys Cys Gln Cys Glu Glu Gly Phe Gln 370 375 380			
Leu Asp Pro His Thr Lys Ala Cys Lys Ala Val Gly Ser Ile Ala Tyr 385 390 395 400			
Leu Phe Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp Arg 405 410 415			
Ser Glu Tyr Thr Ser Leu Ile Pro Asn Leu Arg Asn Val Val Ala Leu 420 425 430			

-continued

---

Asp Thr Glu Val Ala Ser Asn Arg Ile Tyr Trp Ser Asp Leu Ser Gln  
 435 440 445  
 Arg Met Ile Cys Ser Thr Gln Leu Asp Arg Ala His Gly Val Ser Ser  
 450 455 460  
 Tyr Asp Thr Val Ile Ser Arg Asp Ile Gln Ala Pro Asp Gly Leu Ala  
 465 470 475 480  
 Val Asp Trp Ile His Ser Asn Ile Tyr Trp Thr Asp Ser Val Leu Gly  
 485 490 495  
 Thr Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Lys Thr Leu Phe  
 500 505 510  
 Arg Glu Asn Gly Ser Lys Pro Arg Ala Ile Val Val Asp Pro Val His  
 515 520 525  
 Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys  
 530 535 540  
 Gly Gly Leu Asn Gly Val Asp Ile Tyr Ser Leu Val Thr Glu Asn Ile  
 545 550 555 560  
 Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Leu Ser Gly Arg Leu Tyr  
 565 570 575  
 Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly  
 580 585 590  
 Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Lys Arg Leu Ala His Pro  
 595 600 605  
 Phe Ser Leu Ala Val Phe Glu Asp Lys Val Phe Trp Thr Asp Ile Ile  
 610 615 620  
 Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn  
 625 630 635 640  
 Leu Leu Ala Glu Asn Leu Leu Ser Pro Glu Asp Met Val Leu Phe His  
 645 650 655  
 Asn Leu Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Arg Thr Thr Leu  
 660 665 670  
 Ser Asn Gly Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile Asn  
 675 680 685  
 Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu Leu  
 690 695 700  
 Ala Arg Asp Met Arg Ser Cys Leu Thr Glu Ala Glu Ala Ala Val Ala  
 705 710 715 720  
 Thr Gln Glu Thr Ser Thr Val Arg Leu Lys Val Ser Ser Thr Ala Val  
 725 730 735  
 Arg Thr Gln His Thr Thr Thr Arg Pro Val Pro Asp Thr Ser Arg Leu  
 740 745 750  
 Pro Gly Ala Thr Pro Gly Leu Thr Thr Val Glu Ile Val Thr Met Ser  
 755 760 765  
 His Gln Ala Leu Gly Asp Val Ala Gly Arg Gly Asn Glu Lys Lys Pro  
 770 775 780  
 Ser Ser Val Arg Ala Leu Ser Ile Val Leu Pro Ile Val Leu Leu Val  
 785 790 795 800  
 Phe Leu Cys Leu Gly Val Phe Leu Leu Trp Lys Asn Trp Arg Leu Lys  
 805 810 815  
 Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr Gln Lys Thr Thr  
 820 825 830  
 Glu Asp Glu Val His Ile Cys His Asn Gln Asp Gly Tyr Ser Tyr Pro  
 835 840 845

-continued

---

Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala  
850 855 860

<210> SEQ ID NO 68  
<211> LENGTH: 800  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Met Gly Thr Ser Ala Leu Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys  
1 5 10 15

Trp Ala Pro Arg Glu Ser Gly Ala Thr Gly Thr Gly Arg Lys Ala Lys  
20 25 30

Cys Glu Pro Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu  
35 40 45

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Val Asp Gly Ser Asp Glu  
50 55 60

Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Asn  
65 70 75 80

Asn Gly Gln Cys Val Pro Ser Arg Trp Lys Cys Asp Gly Asp Pro Asp  
85 90 95

Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr  
100 105 110

Cys Arg Ile His Glu Ile Ser Cys Gly Ala His Ser Thr Gln Cys Ile  
115 120 125

Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Ser Gly Glu  
130 135 140

Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Pro Asp Glu Phe Thr  
145 150 155 160

Cys Ser Ser Gly Arg Cys Ile Ser Arg Asn Phe Val Cys Asn Gly Gln  
165 170 175

Asp Asp Cys Ser Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr  
180 185 190

Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Ile  
195 200 205

Ser Trp Val Cys Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu  
210 215 220

Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro  
225 230 235 240

Ala Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp  
245 250 255

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn  
260 265 270

Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly  
275 280 285

Ser Cys Ile His Gly Ser Arg Gln Cys Asn Gly Ile Arg Asp Cys Val  
290 295 300

Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly  
305 310 315 320

Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Ile Ser Lys  
325 330 335

Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu  
340 345 350

Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser  
355 360 365

-continued

---

His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala  
 370 375 380

Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys  
 385 390 395 400

Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly  
 405 410 415

Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly  
 420 425 430

Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg  
 435 440 445

Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu  
 450 455 460

Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala  
 465 470 475 480

Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala  
 485 490 495

Ser Ile Asp Asp Lys Val Gly Arg His Val Lys Met Ile Asp Asn Val  
 500 505 510

Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr  
 515 520 525

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly  
 530 535 540

Thr Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser  
 545 550 555 560

Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly  
 565 570 575

Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg  
 580 585 590

Pro Leu Val Thr Ala Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp  
 595 600 605

Leu Ile Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu  
 610 615 620

Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser  
 625 630 635 640

Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg  
 645 650 655

Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys  
 660 665 670

Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala  
 675 680 685

Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn  
 690 695 700

Trp Cys Glu Glu Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu  
 705 710 715 720

Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys  
 725 730 735

Pro Ser Gly Tyr Asn Val Glu Glu Asn Gly Arg Asp Cys Gln Arg Ile  
 740 745 750

Asn Val Thr Thr Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr  
 755 760 765

Ser Ala Ala Trp Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala  
 770 775 780

-continued

---

Val Gly Gly Tyr Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys  
785 790 795 800

<210> SEQ ID NO 69

<211> LENGTH: 873

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Met Gly Thr Ser Ala Leu Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys  
1 5 10 15

Trp Ala Pro Arg Glu Ser Gly Ala Thr Gly Thr Gly Arg Lys Ala Lys  
20 25 30

Cys Glu Pro Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu  
35 40 45

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Val Asp Gly Ser Asp Glu  
50 55 60

Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Asn  
65 70 75 80

Asn Gly Gln Cys Val Pro Ser Arg Trp Lys Cys Asp Gly Asp Pro Asp  
85 90 95

Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr  
100 105 110

Cys Arg Ile His Glu Ile Ser Cys Gly Ala His Ser Thr Gln Cys Ile  
115 120 125

Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Ser Gly Glu  
130 135 140

Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Pro Asp Glu Phe Thr  
145 150 155 160

Cys Ser Ser Gly Arg Cys Ile Ser Arg Asn Phe Val Cys Asn Gly Gln  
165 170 175

Asp Asp Cys Ser Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr  
180 185 190

Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Ile  
195 200 205

Ser Trp Val Cys Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu  
210 215 220

Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro  
225 230 235 240

Ala Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp  
245 250 255

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn  
260 265 270

Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly  
275 280 285

Ser Cys Ile His Gly Ser Arg Gln Cys Asn Gly Ile Arg Asp Cys Val  
290 295 300

Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly  
305 310 315 320

Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Ile Ser Lys  
325 330 335

Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu  
340 345 350

Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser  
355 360 365

-continued

---

His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala  
 370 375 380

Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys  
 385 390 395 400

Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly  
 405 410 415

Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly  
 420 425 430

Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg  
 435 440 445

Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu  
 450 455 460

Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala  
 465 470 475 480

Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala  
 485 490 495

Ser Ile Asp Asp Lys Val Gly Arg His Val Lys Met Ile Asp Asn Val  
 500 505 510

Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr  
 515 520 525

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly  
 530 535 540

Thr Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser  
 545 550 555 560

Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly  
 565 570 575

Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg  
 580 585 590

Pro Leu Val Thr Ala Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp  
 595 600 605

Leu Ile Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu  
 610 615 620

Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser  
 625 630 635 640

Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg  
 645 650 655

Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys  
 660 665 670

Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala  
 675 680 685

Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn  
 690 695 700

Trp Cys Glu Glu Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu  
 705 710 715 720

Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys  
 725 730 735

Pro Ser Gly Tyr Asn Val Glu Glu Asn Gly Arg Asp Cys Gln Ser Thr  
 740 745 750

Ala Thr Thr Val Thr Tyr Ser Glu Thr Lys Asp Thr Asn Thr Thr Glu  
 755 760 765

Ile Ser Ala Thr Ser Gly Leu Val Pro Gly Gly Ile Asn Val Thr Thr  
 770 775 780



-continued

---

Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr Ser Ala Ala Trp  
785 790 795 800

Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala Val Gly Gly Tyr  
805 810 815

Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys Ser Met Asn Phe  
820 825 830

Asp Asn Pro Val Tyr Leu Lys Thr Thr Glu Glu Asp Leu Ser Ile Asp  
835 840 845

Ile Gly Arg His Ser Ala Ser Val Gly His Thr Tyr Pro Ala Ile Ser  
850 855 860

Val Val Ser Thr Asp Asp Asp Leu Ala  
865 870

<210> SEQ ID NO 70  
<211> LENGTH: 1255  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu  
1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys  
20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His  
35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr  
50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu  
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr  
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro  
115 120 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser  
130 135 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln  
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn  
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser  
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
275 280 285

-continued

---

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
 325 330 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu  
 340 345 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys  
 355 360 365

Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp  
 370 375 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe  
 385 390 395 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro  
 405 410 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg  
 420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu  
 435 440 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly  
 450 455 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val  
 465 470 475 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr  
 485 490 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His  
 500 505 510

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys  
 515 520 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys  
 530 535 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys  
 545 550 555 560

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys  
 565 570 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp  
 580 585 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu  
 595 600 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln  
 610 615 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys  
 625 630 635 640

Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Ile Ser  
 645 650 655

Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly  
 660 665 670

Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg  
 675 680 685

Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly  
 690 695 700

-continued

---

Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu  
705 710 715 720

Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys  
725 730 735

Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile  
740 745 750

Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu  
755 760 765

Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg  
770 775 780

Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu  
785 790 795 800

Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg  
805 810 815

Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly  
820 825 830

Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala  
835 840 845

Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe  
850 855 860

Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp  
865 870 875 880

Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg  
885 890 895

Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val  
900 905 910

Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala  
915 920 925

Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro  
930 935 940

Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met  
945 950 955 960

Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe  
965 970 975

Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu  
980 985 990

Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu  
995 1000 1005

Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr  
1010 1015 1020

Leu Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly  
1025 1030 1035

Ala Gly Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg  
1040 1045 1050

Ser Gly Gly Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu  
1055 1060 1065

Glu Ala Pro Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser  
1070 1075 1080

Asp Val Phe Asp Gly Asp Leu Gly Met Gly Ala Ala Lys Gly Leu  
1085 1090 1095

Gln Ser Leu Pro Thr His Asp Pro Ser Pro Leu Gln Arg Tyr Ser  
1100 1105 1110

Glu Asp Pro Thr Val Pro Leu Pro Ser Glu Thr Asp Gly Tyr Val

-continued

1115	1120	1125
Ala Pro Leu Thr Cys Ser Pro Gln Pro Glu Tyr Val Asn Gln Pro 1130	1135	1140
Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro Leu Pro 1145	1150	1155
Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Pro Lys Thr Leu 1160	1165	1170
Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val Phe Ala Phe Gly 1175	1180	1185
Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln Gly Gly Ala 1190	1195	1200
Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala Phe Asp 1205	1210	1215
Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala Pro 1220	1225	1230
Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr 1235	1240	1245
Leu Gly Leu Asp Val Pro Val 1250	1255	

<210> SEQ ID NO 71  
 <211> LENGTH: 1225  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Met Lys Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu 1	5	10	15
Arg His Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu 20	25	30	
Thr Tyr Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln 35	40	45	
Glu Val Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val 50	55	60	
Pro Leu Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp 65	70	75	80
Asn Tyr Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr 85	90	95	
Thr Pro Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu 100	105	110	
Arg Ser Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn 115	120	125	
Pro Gln Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His 130	135	140	
Lys Asn Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg 145	150	155	160
Ala Cys His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly 165	170	175	
Glu Ser Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly 180	185	190	
Gly Cys Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu 195	200	205	
Gln Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala 210	215	220	

-continued

---

Cys Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala  
 225 230 235 240  
 Leu Val Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu  
 245 250 255  
 Gly Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn  
 260 265 270  
 Tyr Leu Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His  
 275 280 285  
 Asn Gln Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys  
 290 295 300  
 Ser Lys Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu  
 305 310 315 320  
 Arg Glu Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly  
 325 330 335  
 Cys Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp  
 340 345 350  
 Gly Asp Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln  
 355 360 365  
 Val Phe Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala  
 370 375 380  
 Trp Pro Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val  
 385 390 395 400  
 Ile Arg Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln  
 405 410 415  
 Gly Leu Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly  
 420 425 430  
 Ser Gly Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His  
 435 440 445  
 Thr Val Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu  
 450 455 460  
 His Thr Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala  
 465 470 475 480  
 Cys His Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr  
 485 490 495  
 Gln Cys Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu  
 500 505 510  
 Glu Cys Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg  
 515 520 525  
 His Cys Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val  
 530 535 540  
 Thr Cys Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr  
 545 550 555 560  
 Lys Asp Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro  
 565 570 575  
 Asp Leu Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala  
 580 585 590  
 Cys Gln Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp  
 595 600 605  
 Asp Lys Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile  
 610 615 620  
 Ile Ser Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val  
 625 630 635 640  
 Phe Gly Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr

-continued

645					650					655					
Met	Arg	Arg	Leu	Leu	Gln	Glu	Thr	Glu	Leu	Val	Glu	Pro	Leu	Thr	Pro
			660					665					670		
Ser	Gly	Ala	Met	Pro	Asn	Gln	Ala	Gln	Met	Arg	Ile	Leu	Lys	Glu	Thr
		675					680					685			
Glu	Leu	Arg	Lys	Val	Lys	Val	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Thr	Val
	690					695					700				
Tyr	Lys	Gly	Ile	Trp	Ile	Pro	Asp	Gly	Glu	Asn	Val	Lys	Ile	Pro	Val
705					710					715					720
Ala	Ile	Lys	Val	Leu	Arg	Glu	Asn	Thr	Ser	Pro	Lys	Ala	Asn	Lys	Glu
			725						730					735	
Ile	Leu	Asp	Glu	Ala	Tyr	Val	Met	Ala	Gly	Val	Gly	Ser	Pro	Tyr	Val
		740						745					750		
Ser	Arg	Leu	Leu	Gly	Ile	Cys	Leu	Thr	Ser	Thr	Val	Gln	Leu	Val	Thr
		755					760					765			
Gln	Leu	Met	Pro	Tyr	Gly	Cys	Leu	Leu	Asp	His	Val	Arg	Glu	Asn	Arg
	770					775					780				
Gly	Arg	Leu	Gly	Ser	Gln	Asp	Leu	Leu	Asn	Trp	Cys	Met	Gln	Ile	Ala
785					790					795					800
Lys	Gly	Met	Ser	Tyr	Leu	Glu	Asp	Val	Arg	Leu	Val	His	Arg	Asp	Leu
			805						810					815	
Ala	Ala	Arg	Asn	Val	Leu	Val	Lys	Ser	Pro	Asn	His	Val	Lys	Ile	Thr
			820					825					830		
Asp	Phe	Gly	Leu	Ala	Arg	Leu	Leu	Asp	Ile	Asp	Glu	Thr	Glu	Tyr	His
	835						840					845			
Ala	Asp	Gly	Gly	Lys	Val	Pro	Ile	Lys	Trp	Met	Ala	Leu	Glu	Ser	Ile
	850					855					860				
Leu	Arg	Arg	Arg	Phe	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Val
865					870					875					880
Thr	Val	Trp	Glu	Leu	Met	Thr	Phe	Gly	Ala	Lys	Pro	Tyr	Asp	Gly	Ile
			885						890					895	
Pro	Ala	Arg	Glu	Ile	Pro	Asp	Leu	Leu	Glu	Lys	Gly	Glu	Arg	Leu	Pro
			900					905						910	
Gln	Pro	Pro	Ile	Cys	Thr	Ile	Asp	Val	Tyr	Met	Ile	Met	Val	Lys	Cys
	915						920					925			
Trp	Met	Ile	Asp	Ser	Glu	Cys	Arg	Pro	Arg	Phe	Arg	Glu	Leu	Val	Ser
930						935					940				
Glu	Phe	Ser	Arg	Met	Ala	Arg	Asp	Pro	Gln	Arg	Phe	Val	Val	Ile	Gln
945					950					955					960
Asn	Glu	Asp	Leu	Gly	Pro	Ala	Ser	Pro	Leu	Asp	Ser	Thr	Phe	Tyr	Arg
				965					970					975	
Ser	Leu	Leu	Glu	Asp	Asp	Asp	Met	Gly	Asp	Leu	Val	Asp	Ala	Glu	Glu
			980					985					990		
Tyr	Leu	Val	Pro	Gln	Gln	Gly	Phe	Phe	Cys	Pro	Asp	Pro	Ala	Pro	Gly
		995					1000						1005		
Ala	Gly	Gly	Met	Val	His	His	Arg	His	Arg	Ser	Ser	Ser	Thr	Arg	
	1010						1015					1020			
Ser	Gly	Gly	Gly	Asp	Leu	Thr	Leu	Gly	Leu	Glu	Pro	Ser	Glu	Glu	
	1025					1030					1035				
Glu	Ala	Pro	Arg	Ser	Pro	Leu	Ala	Pro	Ser	Glu	Gly	Ala	Gly	Ser	
	1040					1045					1050				
Asp	Val	Phe	Asp	Gly	Asp	Leu	Gly	Met	Gly	Ala	Ala	Lys	Gly	Leu	
	1055					1060					1065				

-continued

Gln Ser Leu Pro Thr His Asp Pro Ser Pro Leu Gln Arg Tyr Ser  
 1070 1075 1080  
 Glu Asp Pro Thr Val Pro Leu Pro Ser Glu Thr Asp Gly Tyr Val  
 1085 1090 1095  
 Ala Pro Leu Thr Cys Ser Pro Gln Pro Glu Tyr Val Asn Gln Pro  
 1100 1105 1110  
 Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro Leu Pro  
 1115 1120 1125  
 Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Pro Lys Thr Leu  
 1130 1135 1140  
 Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val Phe Ala Phe Gly  
 1145 1150 1155  
 Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln Gly Gly Ala  
 1160 1165 1170  
 Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala Phe Asp  
 1175 1180 1185  
 Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala Pro  
 1190 1195 1200  
 Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr  
 1205 1210 1215  
 Leu Gly Leu Asp Val Pro Val  
 1220 1225

&lt;210&gt; SEQ ID NO 72

&lt;211&gt; LENGTH: 654

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 72

Met Lys Leu Ser Leu Val Ala Ala Met Leu Leu Leu Leu Ser Ala Ala  
 1 5 10 15  
 Arg Ala Glu Glu Glu Asp Lys Lys Glu Asp Val Gly Thr Val Val Gly  
 20 25 30  
 Ile Asp Leu Gly Thr Thr Tyr Ser Cys Val Gly Val Phe Lys Asn Gly  
 35 40 45  
 Arg Val Glu Ile Ile Ala Asn Asp Gln Gly Asn Arg Ile Thr Pro Ser  
 50 55 60  
 Tyr Val Ala Phe Thr Pro Glu Gly Glu Arg Leu Ile Gly Asp Ala Ala  
 65 70 75 80  
 Lys Asn Gln Leu Thr Ser Asn Pro Glu Asn Thr Val Phe Asp Ala Lys  
 85 90 95  
 Arg Leu Ile Gly Arg Thr Trp Asn Asp Pro Ser Val Gln Gln Asp Ile  
 100 105 110  
 Lys Phe Leu Pro Phe Lys Val Val Glu Lys Lys Thr Lys Pro Tyr Ile  
 115 120 125  
 Gln Val Asp Ile Gly Gly Gly Gln Thr Lys Thr Phe Ala Pro Glu Glu  
 130 135 140  
 Ile Ser Ala Met Val Leu Thr Lys Met Lys Glu Thr Ala Glu Ala Tyr  
 145 150 155 160  
 Leu Gly Lys Lys Val Thr His Ala Val Val Thr Val Pro Ala Tyr Phe  
 165 170 175  
 Asn Asp Ala Gln Arg Gln Ala Thr Lys Asp Ala Gly Thr Ile Ala Gly  
 180 185 190  
 Leu Asn Val Met Arg Ile Ile Asn Glu Pro Thr Ala Ala Ala Ile Ala

-continued

195				200				205							
Tyr	Gly	Leu	Asp	Lys	Arg	Glu	Gly	Glu	Lys	Asn	Ile	Leu	Val	Phe	Asp
210						215					220				
Leu	Gly	Gly	Gly	Thr	Phe	Asp	Val	Ser	Leu	Leu	Thr	Ile	Asp	Asn	Gly
225					230					235					240
Val	Phe	Glu	Val	Val	Ala	Thr	Asn	Gly	Asp	Thr	His	Leu	Gly	Gly	Glu
				245					250					255	
Asp	Phe	Asp	Gln	Arg	Val	Met	Glu	His	Phe	Ile	Lys	Leu	Tyr	Lys	Lys
			260					265					270		
Lys	Thr	Gly	Lys	Asp	Val	Arg	Lys	Asp	Asn	Arg	Ala	Val	Gln	Lys	Leu
		275					280					285			
Arg	Arg	Glu	Val	Glu	Lys	Ala	Lys	Arg	Ala	Leu	Ser	Ser	Gln	His	Gln
		290				295					300				
Ala	Arg	Ile	Glu	Ile	Glu	Ser	Phe	Tyr	Glu	Gly	Glu	Asp	Phe	Ser	Glu
305					310					315					320
Thr	Leu	Thr	Arg	Ala	Lys	Phe	Glu	Glu	Leu	Asn	Met	Asp	Leu	Phe	Arg
				325					330					335	
Ser	Thr	Met	Lys	Pro	Val	Gln	Lys	Val	Leu	Glu	Asp	Ser	Asp	Leu	Lys
			340					345					350		
Lys	Ser	Asp	Ile	Asp	Glu	Ile	Val	Leu	Val	Gly	Gly	Ser	Thr	Arg	Ile
		355					360						365		
Pro	Lys	Ile	Gln	Gln	Leu	Val	Lys	Glu	Phe	Phe	Asn	Gly	Lys	Glu	Pro
		370				375					380				
Ser	Arg	Gly	Ile	Asn	Pro	Asp	Glu	Ala	Val	Ala	Tyr	Gly	Ala	Ala	Val
385					390					395					400
Gln	Ala	Gly	Val	Leu	Ser	Gly	Asp	Gln	Asp	Thr	Gly	Asp	Leu	Val	Leu
				405					410					415	
Leu	Asp	Val	Cys	Pro	Leu	Thr	Leu	Gly	Ile	Glu	Thr	Val	Gly	Gly	Val
			420					425					430		
Met	Thr	Lys	Leu	Ile	Pro	Arg	Asn	Thr	Val	Val	Pro	Thr	Lys	Lys	Ser
		435					440					445			
Gln	Ile	Phe	Ser	Thr	Ala	Ser	Asp	Asn	Gln	Pro	Thr	Val	Thr	Ile	Lys
		450				455					460				
Val	Tyr	Glu	Gly	Glu	Arg	Pro	Leu	Thr	Lys	Asp	Asn	His	Leu	Leu	Gly
465					470					475					480
Thr	Phe	Asp	Leu	Thr	Gly	Ile	Pro	Pro	Ala	Pro	Arg	Gly	Val	Pro	Gln
				485					490					495	
Ile	Glu	Val	Thr	Phe	Glu	Ile	Asp	Val	Asn	Gly	Ile	Leu	Arg	Val	Thr
			500					505					510		
Ala	Glu	Asp	Lys	Gly	Thr	Gly	Asn	Lys	Asn	Lys	Ile	Thr	Ile	Thr	Asn
		515					520					525			
Asp	Gln	Asn	Arg	Leu	Thr	Pro	Glu	Glu	Ile	Glu	Arg	Met	Val	Asn	Asp
		530				535					540				
Ala	Glu	Lys	Phe	Ala	Glu	Glu	Asp	Lys	Lys	Leu	Lys	Glu	Arg	Ile	Asp
545					550					555					560
Thr	Arg	Asn	Glu	Leu	Glu	Ser	Tyr	Ala	Tyr	Ser	Leu	Lys	Asn	Gln	Ile
				565					570					575	
Gly	Asp	Lys	Glu	Lys	Leu	Gly	Gly	Lys	Leu	Ser	Ser	Glu	Asp	Lys	Glu
			580					585					590		
Thr	Met	Glu	Lys	Ala	Val	Glu	Glu	Lys	Ile	Glu	Trp	Leu	Glu	Ser	His
		595					600					605			
Gln	Asp	Ala	Asp	Ile	Glu	Asp	Phe	Lys	Ala	Lys	Lys	Lys	Glu	Leu	Glu
		610				615					620				



-continued

Glu Ile Val Gln Pro Ile Ile Ser Lys Leu Tyr Gly Ser Ala Gly Pro  
625 630 635 640

Pro Pro Thr Gly Glu Glu Asp Thr Ala Glu Lys Asp Glu Leu  
645 650

<210> SEQ ID NO 73

<211> LENGTH: 493

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Met Ser Lys Gly Pro Ala Val Gly Ile Asp Leu Gly Thr Thr Tyr Ser  
1 5 10 15

Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp  
20 25 30

Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu  
35 40 45

Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Met Asn Pro Thr  
50 55 60

Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Arg Phe Asp Asp  
65 70 75 80

Ala Val Val Gln Ser Asp Met Lys His Trp Pro Phe Met Val Val Asn  
85 90 95

Asp Ala Gly Arg Pro Lys Val Gln Val Glu Tyr Lys Gly Glu Thr Lys  
100 105 110

Ser Phe Tyr Pro Glu Glu Val Ser Ser Met Val Leu Thr Lys Met Lys  
115 120 125

Glu Ile Ala Glu Ala Tyr Leu Gly Lys Thr Val Thr Asn Ala Val Val  
130 135 140

Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp  
145 150 155 160

Ala Gly Thr Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro  
165 170 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Lys Lys Val Gly Ala Glu  
180 185 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser  
195 200 205

Ile Leu Thr Ile Glu Asp Gly Ile Phe Glu Val Lys Ser Thr Ala Gly  
210 215 220

Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Met Val Asn His  
225 230 235 240

Phe Ile Ala Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Glu Asn  
245 250 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg  
260 265 270

Thr Leu Ser Ser Ser Thr Gln Ala Ser Ile Glu Ile Asp Ser Leu Tyr  
275 280 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu  
290 295 300

Leu Asn Ala Asp Leu Phe Arg Gly Thr Leu Asp Pro Val Glu Lys Ala  
305 310 315 320

Leu Arg Asp Ala Lys Leu Asp Lys Ser Gln Ile His Asp Ile Val Leu  
325 330 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Ile Gln Lys Leu Leu Gln Asp

-continued

340				345				350							
Phe	Phe	Asn	Gly	Lys	Glu	Leu	Asn	Lys	Ser	Ile	Asn	Pro	Asp	Glu	Ala
		355					360					365			
Val	Ala	Tyr	Gly	Ala	Ala	Val	Gln	Ala	Ala	Ile	Leu	Ser	Gly	Asp	Lys
		370				375					380				
Ser	Glu	Asn	Val	Gln	Asp	Leu	Leu	Leu	Leu	Asp	Val	Thr	Pro	Leu	Ser
		385			390					395					400
Leu	Gly	Ile	Glu	Thr	Ala	Gly	Gly	Val	Met	Thr	Val	Leu	Ile	Lys	Arg
			405						410					415	
Asn	Thr	Thr	Ile	Pro	Thr	Lys	Gln	Thr	Gln	Thr	Phe	Thr	Thr	Tyr	Ser
			420						425					430	
Asp	Asn	Gln	Pro	Gly	Val	Leu	Ile	Gln	Val	Tyr	Glu	Gly	Glu	Arg	Ala
		435					440					445			
Met	Thr	Lys	Asp	Asn	Asn	Leu	Leu	Gly	Lys	Phe	Glu	Leu	Thr	Gly	Met
		450				455					460				
Pro	Gly	Gly	Met	Pro	Gly	Gly	Phe	Pro	Gly	Gly	Gly	Ala	Pro	Pro	Ser
			465		470					475					480
Gly	Gly	Ala	Ser	Ser	Gly	Pro	Thr	Ile	Glu	Glu	Val	Asp			
			485						490						
<210> SEQ ID NO 74															
<211> LENGTH: 646															
<212> TYPE: PRT															
<213> ORGANISM: Homo sapiens															
<400> SEQUENCE: 74															
Met	Ser	Lys	Gly	Pro	Ala	Val	Gly	Ile	Asp	Leu	Gly	Thr	Thr	Tyr	Ser
1				5					10					15	
Cys	Val	Gly	Val	Phe	Gln	His	Gly	Lys	Val	Glu	Ile	Ile	Ala	Asn	Asp
			20					25					30		
Gln	Gly	Asn	Arg	Thr	Thr	Pro	Ser	Tyr	Val	Ala	Phe	Thr	Asp	Thr	Glu
		35					40					45			
Arg	Leu	Ile	Gly	Asp	Ala	Ala	Lys	Asn	Gln	Val	Ala	Met	Asn	Pro	Thr
		50				55					60				
Asn	Thr	Val	Phe	Asp	Ala	Lys	Arg	Leu	Ile	Gly	Arg	Arg	Phe	Asp	Asp
		65			70					75				80	
Ala	Val	Val	Gln	Ser	Asp	Met	Lys	His	Trp	Pro	Phe	Met	Val	Val	Asn
			85						90					95	
Asp	Ala	Gly	Arg	Pro	Lys	Val	Gln	Val	Glu	Tyr	Lys	Gly	Glu	Thr	Lys
			100						105				110		
Ser	Phe	Tyr	Pro	Glu	Glu	Val	Ser	Ser	Met	Val	Leu	Thr	Lys	Met	Lys
		115					120					125			
Glu	Ile	Ala	Glu	Ala	Tyr	Leu	Gly	Lys	Thr	Val	Thr	Asn	Ala	Val	Val
		130				135					140				
Thr	Val	Pro	Ala	Tyr	Phe	Asn	Asp	Ser	Gln	Arg	Gln	Ala	Thr	Lys	Asp
		145			150					155				160	
Ala	Gly	Thr	Ile	Ala	Gly	Leu	Asn	Val	Leu	Arg	Ile	Ile	Asn	Glu	Pro
			165						170				175		
Thr	Ala	Ala	Ala	Ile	Ala	Tyr	Gly	Leu	Asp	Lys	Lys	Val	Gly	Ala	Glu
			180						185				190		
Arg	Asn	Val	Leu	Ile	Phe	Asp	Leu	Gly	Gly	Gly	Thr	Phe	Asp	Val	Ser
		195					200					205			
Ile	Leu	Thr	Ile	Glu	Asp	Gly	Ile	Phe	Glu	Val	Lys	Ser	Thr	Ala	Gly
		210				215					220				



-continued

645

<210> SEQ ID NO 75  
 <211> LENGTH: 188  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Met Ala Leu Thr Phe Ala Leu Leu Val Ala Leu Leu Val Leu Ser Cys  
 1 5 10 15  
 Lys Ser Ser Cys Ser Val Gly Cys Asp Leu Pro Gln Thr His Ser Leu  
 20 25 30  
 Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser  
 35 40 45  
 Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu  
 50 55 60  
 Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His  
 65 70 75 80  
 Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser  
 85 90 95  
 Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr  
 100 105 110  
 Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val  
 115 120 125  
 Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys  
 130 135 140  
 Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro  
 145 150 155 160  
 Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu  
 165 170 175  
 Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu  
 180 185

<210> SEQ ID NO 76  
 <211> LENGTH: 153  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu  
 1 5 10 15  
 Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu  
 20 25 30  
 Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile  
 35 40 45  
 Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe  
 50 55 60  
 Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu  
 65 70 75 80  
 Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys  
 85 90 95  
 Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile  
 100 105 110  
 Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala  
 115 120 125  
 Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe



-continued

---

Ala Val Val Asn Gln Tyr Arg Met Arg Gly Leu Asn Pro Gly Thr Val  
 355 360 365

Asn Ser Cys Cys Ile Pro Thr Lys Leu Ser Thr Met Ser Met Leu Tyr  
 370 375 380

Phe Asp Asp Glu Tyr Asn Ile Val Lys Arg Asp Val Pro Asn Met Ile  
 385 390 395 400

Val Glu Glu Cys Gly Cys Ala  
 405

<210> SEQ ID NO 78  
 <211> LENGTH: 582  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Met Ser Pro Ala Pro Arg Pro Pro Arg Cys Leu Leu Leu Pro Leu Leu  
 1 5 10 15

Thr Leu Gly Thr Ala Leu Ala Ser Leu Gly Ser Ala Gln Ser Ser Ser  
 20 25 30

Phe Ser Pro Glu Ala Trp Leu Gln Gln Tyr Gly Tyr Leu Pro Pro Gly  
 35 40 45

Asp Leu Arg Thr His Thr Gln Arg Ser Pro Gln Ser Leu Ser Ala Ala  
 50 55 60

Ile Ala Ala Met Gln Lys Phe Tyr Gly Leu Gln Val Thr Gly Lys Ala  
 65 70 75 80

Asp Ala Asp Thr Met Lys Ala Met Arg Arg Pro Arg Cys Gly Val Pro  
 85 90 95

Asp Lys Phe Gly Ala Glu Ile Lys Ala Asn Val Arg Arg Lys Arg Tyr  
 100 105 110

Ala Ile Gln Gly Leu Lys Trp Gln His Asn Glu Ile Thr Phe Cys Ile  
 115 120 125

Gln Asn Tyr Thr Pro Lys Val Gly Glu Tyr Ala Thr Tyr Glu Ala Ile  
 130 135 140

Arg Lys Ala Phe Arg Val Trp Glu Ser Ala Thr Pro Leu Arg Phe Arg  
 145 150 155 160

Glu Val Pro Tyr Ala Tyr Ile Arg Glu Gly His Glu Lys Gln Ala Asp  
 165 170 175

Ile Met Ile Phe Phe Ala Glu Gly Phe His Gly Asp Ser Thr Pro Phe  
 180 185 190

Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Asn  
 195 200 205

Ile Gly Gly Asp Thr His Phe Asp Ser Ala Glu Pro Trp Thr Val Arg  
 210 215 220

Asn Glu Asp Leu Asn Gly Asn Asp Ile Phe Leu Val Ala Val His Glu  
 225 230 235 240

Leu Gly His Ala Leu Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile  
 245 250 255

Met Ala Pro Phe Tyr Gln Trp Met Asp Thr Glu Asn Phe Val Leu Pro  
 260 265 270

Asp Asp Asp Arg Arg Gly Ile Gln Gln Leu Tyr Gly Gly Glu Ser Gly  
 275 280 285

Phe Pro Thr Lys Met Pro Pro Gln Pro Arg Thr Thr Ser Arg Pro Ser  
 290 295 300

Val Pro Asp Lys Pro Lys Asn Pro Thr Tyr Gly Pro Asn Ile Cys Asp  
 305 310 315 320

-continued

Gly Asn Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met Phe Val Phe  
 325 330 335  
 Lys Glu Arg Trp Phe Trp Arg Val Arg Asn Asn Gln Val Met Asp Gly  
 340 345 350  
 Tyr Pro Met Pro Ile Gly Gln Phe Trp Arg Gly Leu Pro Ala Ser Ile  
 355 360 365  
 Asn Thr Ala Tyr Glu Arg Lys Asp Gly Lys Phe Val Phe Phe Lys Gly  
 370 375 380  
 Asp Lys His Trp Val Phe Asp Glu Ala Ser Leu Glu Pro Gly Tyr Pro  
 385 390 395 400  
 Lys His Ile Lys Glu Leu Gly Arg Gly Leu Pro Thr Asp Lys Ile Asp  
 405 410 415  
 Ala Ala Leu Phe Trp Met Pro Asn Gly Lys Thr Tyr Phe Phe Arg Gly  
 420 425 430  
 Asn Lys Tyr Tyr Arg Phe Asn Glu Glu Leu Arg Ala Val Asp Ser Glu  
 435 440 445  
 Tyr Pro Lys Asn Ile Lys Val Trp Glu Gly Ile Pro Glu Ser Pro Arg  
 450 455 460  
 Gly Ser Phe Met Gly Ser Asp Glu Val Phe Thr Tyr Phe Tyr Lys Gly  
 465 470 475 480  
 Asn Lys Tyr Trp Lys Phe Asn Asn Gln Lys Leu Lys Val Glu Pro Gly  
 485 490 495  
 Tyr Pro Lys Ser Ala Leu Arg Asp Trp Met Gly Cys Pro Ser Gly Gly  
 500 505 510  
 Arg Pro Asp Glu Gly Thr Glu Glu Glu Thr Glu Val Ile Ile Ile Glu  
 515 520 525  
 Val Asp Glu Glu Gly Gly Gly Ala Val Ser Ala Ala Ala Val Val Leu  
 530 535 540  
 Pro Val Leu Leu Leu Leu Leu Val Leu Ala Val Gly Leu Ala Val Phe  
 545 550 555 560  
 Phe Phe Arg Arg His Gly Thr Pro Arg Arg Leu Leu Tyr Cys Gln Arg  
 565 570 575  
 Ser Leu Leu Asp Lys Val  
 580

&lt;210&gt; SEQ ID NO 79

&lt;211&gt; LENGTH: 418

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 79

Met Arg Ala Ala Pro Leu Leu Leu Ala Arg Ala Ala Ser Leu Ser Leu  
 1 5 10 15  
 Gly Phe Leu Phe Leu Leu Phe Phe Trp Leu Asp Arg Ser Val Leu Ala  
 20 25 30  
 Lys Glu Leu Lys Phe Val Thr Leu Val Phe Arg His Gly Asp Arg Ser  
 35 40 45  
 Pro Ile Asp Thr Phe Pro Thr Asp Pro Ile Lys Glu Ser Ser Trp Pro  
 50 55 60  
 Gln Gly Phe Gly Gln Leu Thr Gln Leu Gly Met Glu Gln His Tyr Glu  
 65 70 75 80  
 Leu Gly Glu Tyr Ile Arg Lys Arg Tyr Arg Lys Phe Leu Asn Glu Ser  
 85 90 95  
 Tyr Lys His Glu Gln Val Tyr Ile Arg Ser Thr Asp Val Asp Arg Thr

-continued

100				105				110							
Leu	Met	Ser	Ala	Met	Thr	Asn	Leu	Ala	Ala	Leu	Phe	Pro	Pro	Glu	Gly
		115					120						125		
Val	Ser	Ile	Trp	Asn	Pro	Ile	Leu	Leu	Trp	Gln	Pro	Ile	Pro	Val	His
	130				135					140					
Thr	Val	Pro	Leu	Ser	Glu	Asp	Gln	Leu	Leu	Tyr	Leu	Pro	Phe	Arg	Asn
	145				150					155					160
Cys	Pro	Arg	Phe	Gln	Glu	Leu	Glu	Ser	Glu	Thr	Leu	Lys	Ser	Glu	Glu
			165						170					175	
Phe	Gln	Lys	Arg	Leu	His	Pro	Tyr	Lys	Asp	Phe	Ile	Ala	Thr	Leu	Gly
		180							185				190		
Lys	Leu	Ser	Gly	Leu	His	Gly	Gln	Asp	Leu	Phe	Gly	Ile	Trp	Ser	Lys
	195						200					205			
Val	Tyr	Asp	Pro	Leu	Tyr	Cys	Glu	Ser	Val	His	Asn	Phe	Thr	Leu	Pro
	210					215					220				
Ser	Trp	Ala	Thr	Glu	Asp	Thr	Met	Thr	Lys	Leu	Arg	Glu	Leu	Ser	Glu
	225				230					235					240
Leu	Ser	Leu	Leu	Ser	Leu	Tyr	Gly	Ile	His	Lys	Gln	Lys	Glu	Lys	Ser
			245						250					255	
Arg	Leu	Gln	Gly	Gly	Val	Leu	Val	Asn	Glu	Ile	Leu	Asn	His	Met	Lys
		260							265				270		
Arg	Ala	Thr	Gln	Ile	Pro	Ser	Tyr	Lys	Lys	Leu	Ile	Met	Tyr	Ser	Ala
		275					280						285		
His	Asp	Thr	Thr	Val	Ser	Gly	Leu	Gln	Met	Ala	Leu	Asp	Val	Tyr	Asn
	290					295					300				
Gly	Leu	Leu	Pro	Pro	Tyr	Ala	Ser	Cys	His	Leu	Thr	Glu	Leu	Tyr	Phe
	305				310					315					320
Glu	Lys	Gly	Glu	Tyr	Phe	Val	Glu	Met	Tyr	Tyr	Arg	Asn	Glu	Thr	Gln
			325						330					335	
His	Glu	Pro	Tyr	Pro	Leu	Met	Leu	Pro	Gly	Cys	Ser	Pro	Ser	Cys	Pro
		340							345				350		
Leu	Glu	Arg	Phe	Ala	Glu	Leu	Val	Gly	Pro	Val	Ile	Pro	Gln	Asp	Trp
		355					360						365		
Ser	Thr	Glu	Cys	Met	Thr	Thr	Asn	Ser	His	Gln	Val	Leu	Lys	Val	Ile
	370						375				380				
Phe	Ala	Val	Ala	Phe	Cys	Leu	Ile	Ser	Ala	Val	Leu	Met	Val	Leu	Leu
			385		390					395					400
Phe	Ile	His	Ile	Arg	Arg	Gly	Leu	Cys	Trp	Gln	Arg	Glu	Ser	Tyr	Gly
			405						410					415	

Asn Ile

&lt;210&gt; SEQ ID NO 80

&lt;211&gt; LENGTH: 386

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 80

Met	Arg	Ala	Ala	Pro	Leu	Leu	Leu	Ala	Arg	Ala	Ala	Ser	Leu	Ser	Leu
				5					10				15		
Gly	Phe	Leu	Phe	Leu	Leu	Phe	Phe	Trp	Leu	Asp	Arg	Ser	Val	Leu	Ala
			20						25				30		
Lys	Glu	Leu	Lys	Phe	Val	Thr	Leu	Val	Phe	Arg	His	Gly	Asp	Arg	Ser
		35					40					45			
Pro	Ile	Asp	Thr	Phe	Pro	Thr	Asp	Pro	Ile	Lys	Glu	Ser	Ser	Trp	Pro



-continued

50	55	60
Gln Gly Phe Gly Gln Leu Thr Gln Leu Gly Met Glu Gln His Tyr Glu 65 70 75 80		
Leu Gly Glu Tyr Ile Arg Lys Arg Tyr Arg Lys Phe Leu Asn Glu Ser 85 90 95		
Tyr Lys His Glu Gln Val Tyr Ile Arg Ser Thr Asp Val Asp Arg Thr 100 105 110		
Leu Met Ser Ala Met Thr Asn Leu Ala Ala Leu Phe Pro Pro Glu Gly 115 120 125		
Val Ser Ile Trp Asn Pro Ile Leu Leu Trp Gln Pro Ile Pro Val His 130 135 140		
Thr Val Pro Leu Ser Glu Asp Gln Leu Leu Tyr Leu Pro Phe Arg Asn 145 150 155 160		
Cys Pro Arg Phe Gln Glu Leu Glu Ser Glu Thr Leu Lys Ser Glu Glu 165 170 175		
Phe Gln Lys Arg Leu His Pro Tyr Lys Asp Phe Ile Ala Thr Leu Gly 180 185 190		
Lys Leu Ser Gly Leu His Gly Gln Asp Leu Phe Gly Ile Trp Ser Lys 195 200 205		
Val Tyr Asp Pro Leu Tyr Cys Glu Ser Val His Asn Phe Thr Leu Pro 210 215 220		
Ser Trp Ala Thr Glu Asp Thr Met Thr Lys Leu Arg Glu Leu Ser Glu 225 230 235 240		
Leu Ser Leu Leu Ser Leu Tyr Gly Ile His Lys Gln Lys Glu Lys Ser 245 250 255		
Arg Leu Gln Gly Gly Val Leu Val Asn Glu Ile Leu Asn His Met Lys 260 265 270		
Arg Ala Thr Gln Ile Pro Ser Tyr Lys Lys Leu Ile Met Tyr Ser Ala 275 280 285		
His Asp Thr Thr Val Ser Gly Leu Gln Met Ala Leu Asp Val Tyr Asn 290 295 300		
Gly Leu Leu Pro Pro Tyr Ala Ser Cys His Leu Thr Glu Leu Tyr Phe 305 310 315 320		
Glu Lys Gly Glu Tyr Phe Val Glu Met Tyr Tyr Arg Asn Glu Thr Gln 325 330 335		
His Glu Pro Tyr Pro Leu Met Leu Pro Gly Cys Ser Pro Ser Cys Pro 340 345 350		
Leu Glu Arg Phe Ala Glu Leu Val Gly Pro Val Ile Pro Gln Asp Trp 355 360 365		
Ser Thr Glu Cys Met Thr Thr Asn Ser His Gln Gly Thr Glu Asp Ser 370 375 380		
Thr Asp 385		

<210> SEQ ID NO 81  
 <211> LENGTH: 646  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Met Gly Leu Pro Arg Leu Val Cys Ala Phe Leu Leu Ala Ala Cys Cys 1 5 10 15
Cys Cys Pro Arg Val Ala Gly Val Pro Gly Glu Ala Glu Gln Pro Ala 20 25 30

-continued

---

Pro	Glu	Leu	Val	Glu	Val	Glu	Val	Gly	Ser	Thr	Ala	Leu	Leu	Lys	Cys
		35					40					45			
Gly	Leu	Ser	Gln	Ser	Gln	Gly	Asn	Leu	Ser	His	Val	Asp	Trp	Phe	Ser
	50					55					60				
Val	His	Lys	Glu	Lys	Arg	Thr	Leu	Ile	Phe	Arg	Val	Arg	Gln	Gly	Gln
65					70					75					80
Gly	Gln	Ser	Glu	Pro	Gly	Glu	Tyr	Glu	Gln	Arg	Leu	Ser	Leu	Gln	Asp
				85					90					95	
Arg	Gly	Ala	Thr	Leu	Ala	Leu	Thr	Gln	Val	Thr	Pro	Gln	Asp	Glu	Arg
			100					105					110		
Ile	Phe	Leu	Cys	Gln	Gly	Lys	Arg	Pro	Arg	Ser	Gln	Glu	Tyr	Arg	Ile
		115					120					125			
Gln	Leu	Arg	Val	Tyr	Lys	Ala	Pro	Glu	Glu	Pro	Asn	Ile	Gln	Val	Asn
	130					135					140				
Pro	Leu	Gly	Ile	Pro	Val	Asn	Ser	Lys	Glu	Pro	Glu	Glu	Val	Ala	Thr
145					150					155					160
Cys	Val	Gly	Arg	Asn	Gly	Tyr	Pro	Ile	Pro	Gln	Val	Ile	Trp	Tyr	Lys
				165					170					175	
Asn	Gly	Arg	Pro	Leu	Lys	Glu	Glu	Lys	Asn	Arg	Val	His	Ile	Gln	Ser
			180					185					190		
Ser	Gln	Thr	Val	Glu	Ser	Ser	Gly	Leu	Tyr	Thr	Leu	Gln	Ser	Ile	Leu
		195					200					205			
Lys	Ala	Gln	Leu	Val	Lys	Glu	Asp	Lys	Asp	Ala	Gln	Phe	Tyr	Cys	Glu
	210					215					220				
Leu	Asn	Tyr	Arg	Leu	Pro	Ser	Gly	Asn	His	Met	Lys	Glu	Ser	Arg	Glu
225					230					235					240
Val	Thr	Val	Pro	Val	Phe	Tyr	Pro	Thr	Glu	Lys	Val	Trp	Leu	Glu	Val
				245					250					255	
Glu	Pro	Val	Gly	Met	Leu	Lys	Glu	Gly	Asp	Arg	Val	Glu	Ile	Arg	Cys
			260					265					270		
Leu	Ala	Asp	Gly	Asn	Pro	Pro	Pro	His	Phe	Ser	Ile	Ser	Lys	Gln	Asn
		275					280					285			
Pro	Ser	Thr	Arg	Glu	Ala	Glu	Glu	Glu	Thr	Thr	Asn	Asp	Asn	Gly	Val
		290				295					300				
Leu	Val	Leu	Glu	Pro	Ala	Arg	Lys	Glu	His	Ser	Gly	Arg	Tyr	Glu	Cys
305					310					315					320
Gln	Gly	Leu	Asp	Leu	Asp	Thr	Met	Ile	Ser	Leu	Leu	Ser	Glu	Pro	Gln
				325					330					335	
Glu	Leu	Leu	Val	Asn	Tyr	Val	Ser	Asp	Val	Arg	Val	Ser	Pro	Ala	Ala
			340					345					350		
Pro	Glu	Arg	Gln	Glu	Gly	Ser	Ser	Leu	Thr	Leu	Thr	Cys	Glu	Ala	Glu
		355					360					365			
Ser	Ser	Gln	Asp	Leu	Glu	Phe	Gln	Trp	Leu	Arg	Glu	Glu	Thr	Gly	Gln
		370				375					380				
Val	Leu	Glu	Arg	Gly	Pro	Val	Leu	Gln	Leu	His	Asp	Leu	Lys	Arg	Glu
385					390					395					400
Ala	Gly	Gly	Gly	Tyr	Arg	Cys	Val	Ala	Ser	Val	Pro	Ser	Ile	Pro	Gly
				405					410					415	
Leu	Asn	Arg	Thr	Gln	Leu	Val	Asn	Val	Ala	Ile	Phe	Gly	Pro	Pro	Trp
			420					425					430		
Met	Ala	Phe	Lys	Glu	Arg	Lys	Val	Trp	Val	Lys	Glu	Asn	Met	Val	Leu
		435					440					445			
Asn	Leu	Ser	Cys	Glu	Ala	Ser	Gly	His	Pro	Arg	Pro	Thr	Ile	Ser	Trp

-continued

450	455	460
Asn Val Asn Gly Thr Ala Ser Glu Gln Asp Gln Asp Pro Gln Arg Val 465	470	475 480
Leu Ser Thr Leu Asn Val Leu Val Thr Pro Glu Leu Leu Glu Thr Gly 485	490	495
Val Glu Cys Thr Ala Ser Asn Asp Leu Gly Lys Asn Thr Ser Ile Leu 500	505	510
Phe Leu Glu Leu Val Asn Leu Thr Thr Leu Thr Pro Asp Ser Asn Thr 515	520	525
Thr Thr Gly Leu Ser Thr Ser Thr Ala Ser Pro His Thr Arg Ala Asn 530	535	540
Ser Thr Ser Thr Glu Arg Lys Leu Pro Glu Pro Glu Ser Arg Gly Val 545	550	555 560
Val Ile Val Ala Val Ile Val Cys Ile Leu Val Leu Ala Val Leu Gly 565	570	575
Ala Val Leu Tyr Phe Leu Tyr Lys Lys Gly Lys Leu Pro Cys Arg Arg 580	585	590
Ser Gly Lys Gln Glu Ile Thr Leu Pro Pro Ser Arg Lys Ser Glu Leu 595	600	605
Val Val Glu Val Lys Ser Asp Lys Leu Pro Glu Glu Met Gly Leu Leu 610	615	620
Gln Gly Ser Ser Gly Asp Lys Arg Ala Pro Gly Asp Gln Gly Glu Lys 625	630	635 640
Tyr Ile Asp Leu Arg His 645		

<210> SEQ ID NO 82  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 82

Thr Lys Ala Gly Arg Gly Ala Ser Gln Pro Pro Thr Pro Thr Pro Ala 1	5	10	15
Ser Asp Ala Phe 20			

<210> SEQ ID NO 83  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 83

Glu Glu Glu Pro Glu Glu Thr Ala Glu Asp Thr Thr Glu Asp Thr Glu 1	5	10	15
Gln Asp Glu Asp 20			

<210> SEQ ID NO 84  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 84

-continued

Thr Ala Ser Thr Thr Ala Asn Thr Pro Phe Pro Thr Ala Thr Ser Pro  
1 5 10 15

Ala Pro Pro Ile  
20

<210> SEQ ID NO 85  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 85

Pro Ala Pro Pro Ile Ile Ser Thr His Ser Ser Ser Thr Ile Pro Thr  
1 5 10 15

Pro Ala Pro Pro  
20

<210> SEQ ID NO 86  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 86

Leu Ala Lys Met Tyr Tyr Ser Ala Val Glu Pro Thr Lys Asp Ile Phe  
1 5 10 15

Thr Gly Leu Ile  
20

<210> SEQ ID NO 87  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 87

Pro Ser Ser Thr Lys Pro Pro Ala Leu Ser His Ser Val Ser Thr Ser  
1 5 10 15

Ser Thr Thr Lys  
20

<210> SEQ ID NO 88  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 88

Leu Glu Pro Asp Tyr Phe Lys Asp Met Thr Pro Thr Ile Arg Lys Thr  
1 5 10 15

Gln Lys Ile Val  
20

<210> SEQ ID NO 89  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

-continued

---

<400> SEQUENCE: 89

Ser Thr Met Pro Val Val Ser Ser Glu Ala Ser Thr His Ser Thr Thr  
 1 5 10 15

Pro Val Asp Thr  
 20

<210> SEQ ID NO 90

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 90

Ser Thr His Ser Thr Thr Pro Val Asp Thr Ser Thr Pro Val Thr Thr  
 1 5 10 15

Ser Thr Glu Ala  
 20

<210> SEQ ID NO 91

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 91

Ile Pro Pro Glu Asp Thr Ala Ser Thr Arg Ser Ser Phe Thr Val Gln  
 1 5 10 15

Asp Leu Lys Pro  
 20

<210> SEQ ID NO 92

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 92

Glu Ala Lys Thr Ser Asn Pro Thr Ser Ser Leu Thr Ser Leu Ser Val  
 1 5 10 15

Ala Pro Thr Phe  
 20

<210> SEQ ID NO 93

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 93

Ala Arg Thr Glu Pro Trp Glu Gly Asn Ser Ser Thr Ala Ala Thr Thr  
 1 5 10 15

Pro Glu Thr Phe  
 20

<210> SEQ ID NO 94

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

-continued

&lt;400&gt; SEQUENCE: 94

Val Asp Pro Leu Gln Leu Gln Thr Pro Pro Gln Thr Gln Pro Gly Pro  
 1                   5                   10                   15

Ser His Val Met  
                   20

&lt;210&gt; SEQ ID NO 95

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 95

Ser Pro Lys Pro Ser Thr Thr Asn Val Phe Thr Ser Ala Val Asp Gln  
 1                   5                   10                   15

Thr Ile Thr Pro  
                   20

&lt;210&gt; SEQ ID NO 96

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 96

Pro Ala Pro Pro Ala Pro Gly Asn Ala Ser Glu Ser Glu Glu Asp Arg  
 1                   5                   10                   15

Ser Ala Gly Ser  
                   20

&lt;210&gt; SEQ ID NO 97

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 97

Ala Ser Glu Ser Glu Glu Asp Arg Ser Ala Gly Ser Val Glu Ser Pro  
 1                   5                   10                   15

Ser Val Ser Ser  
                   20

&lt;210&gt; SEQ ID NO 98

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic peptides

&lt;400&gt; SEQUENCE: 98

Ala Asn Leu Asn Ser Asp Lys Glu Asn Ile Thr Thr Ser Asn Leu Lys  
 1                   5                   10                   15

Ala Ser His Ser  
                   20

&lt;210&gt; SEQ ID NO 99

&lt;211&gt; LENGTH: 20

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

-continued

---

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 99

Leu Thr Thr Asn Ser Asp Ser Phe Thr Gly Phe Thr Pro Tyr Gln Glu  
 1 5 10 15

Lys Thr Thr Leu  
 20

<210> SEQ ID NO 100

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 100

Ser Phe Thr Gly Phe Thr Pro Tyr Gln Glu Lys Thr Thr Leu Gln Pro  
 1 5 10 15

Thr Leu Lys Phe  
 20

<210> SEQ ID NO 101

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 101

Ser Phe Thr Gly Phe Thr Pro Tyr Gln Glu Lys Thr Thr Leu Gln Pro  
 1 5 10 15

Thr Leu Lys Phe  
 20

<210> SEQ ID NO 102

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 102

Ser Pro Thr Ser Ser Ala Ser Ser Phe Ser Ser Ser Ala Pro Phe Leu  
 1 5 10 15

Ala Ser Ala Val  
 20

<210> SEQ ID NO 103

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 103

Thr Val Pro Cys Pro Val Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser  
 1 5 10 15

Thr Pro Pro Thr  
 20

<210> SEQ ID NO 104

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

-continued

---

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 104

Val Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro  
1 5 10 15

Ser Pro Ser Cys  
20

<210> SEQ ID NO 105

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 105

Ser Glu Pro Pro Lys Ala Ala Arg Pro Pro Val Thr Pro Val Leu Leu  
1 5 10 15

Glu Lys Lys Ser  
20

<210> SEQ ID NO 106

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 106

Gly Gln Ser Gln Pro Thr Val Ala Gly Gln Pro Ser Ala Arg Pro Ala  
1 5 10 15

Ala Glu Glu Tyr  
20

<210> SEQ ID NO 107

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 107

Thr Pro Ala Ser Ile Thr Ala Ala Lys Thr Ser Thr Ile Thr Thr Ala  
1 5 10 15

Phe Pro Pro Val  
20

<210> SEQ ID NO 108

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 108

Gly Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg  
1 5 10 15

Ser Met Ala Pro  
20

<210> SEQ ID NO 109

<211> LENGTH: 20

<212> TYPE: PRT



-continued

---

<213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 109

Thr Asp Cys Gly Gly Pro Lys Asp His Pro Leu Thr Cys Asp Asp Pro  
 1                   5                   10                   15

Arg Phe Gln Ala  
                   20

<210> SEQ ID NO 110  
 <211> LENGTH: 21  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 110

Ala Gln Ala Ser Ser Ser Ser Lys Ala Pro Pro Pro Ser Leu Pro Ser  
 1                   5                   10                   15

Pro Ser Arg Leu Pro  
                   20

<210> SEQ ID NO 111  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 111

Pro Leu Ser Glu Leu Glu Ser Gly Glu Gln Pro Ser Asp Glu Gln Pro  
 1                   5                   10                   15

Ser Gly Glu His  
                   20

<210> SEQ ID NO 112  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 112

Pro Gln Arg Ser Ser Thr Ala Ile Leu Gln Val Ser Val Thr Asp Thr  
 1                   5                   10                   15

Asn Asp Asn His  
                   20

<210> SEQ ID NO 113  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 113

Gly Ala Leu Pro Gly Thr Ser Val Met Glu Val Thr Ala Thr Asp Ala  
 1                   5                   10                   15

Asp Asp Asp Val  
                   20

<210> SEQ ID NO 114  
 <211> LENGTH: 20

-continued

<212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 114

Glu Gln Glu Pro Pro Ser Thr Asp Val Pro Pro Ser Pro Glu Ala Gly  
 1                   5                   10                   15

Gly Thr Thr Gly  
 20

<210> SEQ ID NO 115  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 115

Arg Pro Glu Ala Thr Pro Phe Leu Val Ala His Thr Arg Thr Arg Pro  
 1                   5                   10                   15

Pro Ser Gly Gly  
 20

<210> SEQ ID NO 116  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 116

Pro Gly Thr Ser Thr Thr Pro Ser Gln Pro Asn Ser Ala Gly Val Gln  
 1                   5                   10                   15

Asp Thr Glu Met  
 20

<210> SEQ ID NO 117  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 117

Glu Val Ala Pro Glu Ala Ser Thr Ser Ser Ala Ser Gln Val Ile Ala  
 1                   5                   10                   15

Pro Thr Gln Val  
 20

<210> SEQ ID NO 118  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 118

Gln Pro Pro Asp Phe Ala Leu Ala Tyr Arg Pro Ser Phe Pro Glu Asp  
 1                   5                   10                   15

Arg Glu Pro Gln  
 20

<210> SEQ ID NO 119

-continued

---

<211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 119

Leu Ser Val Thr Arg Pro Val Val Val Ser Ala Thr His Pro Thr Leu  
 1                   5                   10                   15  
 Pro Ser Ala His  
                   20

<210> SEQ ID NO 120  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 120

Pro Ser Ala His Gln Pro Pro Val Ile Pro Ala Thr His Pro Ala Leu  
 1                   5                   10                   15  
 Ser Arg Asp His  
                   20

<210> SEQ ID NO 121  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 121

Ala Pro Asp Ala Leu Val Leu Arg Thr Gln Ala Thr Gln Leu Pro Ile  
 1                   5                   10                   15  
 Ile Pro Thr Ala  
                   20

<210> SEQ ID NO 122  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 122

Gly Ala Leu Phe Pro Gly Pro Gly Asn Ala Gln Thr Ser Val Ser Pro  
 1                   5                   10                   15  
 Ser Lys Val Ile  
                   20

<210> SEQ ID NO 123  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 123

His Leu Ala Leu Gly Asp Gln Arg Leu Asn Pro Thr Val Thr Tyr Gly  
 1                   5                   10                   15  
 Asn Asp Ser Phe  
                   20

-continued

---

<210> SEQ ID NO 124  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 124

His Leu Ala Leu Gly Asp Gln Arg Leu Asn Pro Thr Val Thr Tyr Gly  
 1                   5                   10                   15

Asn Asp Ser Phe  
                   20

<210> SEQ ID NO 125  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 125

Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln Asp  
 1                   5                   10                   15

Val Thr Ser Val  
                   20

<210> SEQ ID NO 126  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 126

Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His  
 1                   5                   10                   15

Asp Val Thr Ser  
                   20

<210> SEQ ID NO 127  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 127

Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu  
 1                   5                   10                   15

Val His Asn Gly  
                   20

<210> SEQ ID NO 128  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 128

Asn Val Thr Ser Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu  
 1                   5                   10                   15

Val His Asn Gly  
                   20

-continued

<210> SEQ ID NO 129  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 129

Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro  
 1 5 10 15

Phe Ser Ile Pro  
 20

<210> SEQ ID NO 130  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 130

Gly Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro  
 1 5 10 15

Phe Ser Ile Pro  
 20

<210> SEQ ID NO 131  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 131

Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr Asp Ala  
 1 5 10 15

Ser Ser Thr His  
 20

<210> SEQ ID NO 132  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 132

Thr Lys Thr Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu  
 1 5 10 15

Thr Ser Ser Asn  
 20

<210> SEQ ID NO 133  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 133

Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu  
 1 5 10 15

Gln Ile Tyr Lys  
 20

-continued

<210> SEQ ID NO 134  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 134

His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser  
 1                   5                   10                   15

Arg Tyr Asn Leu  
 20

<210> SEQ ID NO 135  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 135

Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val  
 1                   5                   10                   15

Pro Phe Pro Phe  
 20

<210> SEQ ID NO 136  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 136

Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val Pro Phe  
 1                   5                   10                   15

Pro Phe Ser Ala  
 20

<210> SEQ ID NO 137  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 137

Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly  
 1                   5                   10                   15

Ala Gly Val Pro  
 20

<210> SEQ ID NO 138  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 138

Thr Ala Gly Arg Pro Thr Gly Gln Ser Ser Pro Thr Ser Pro Ser Ala  
 1                   5                   10                   15

Ser Pro Gln Glu

-continued

20

<210> SEQ ID NO 139  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 139

Ser Leu Ala Ser Gln Ala Thr Asp Thr Phe Ser Thr Val Pro Pro Thr  
 1 5 10 15

Pro Pro Ser Ile  
 20

<210> SEQ ID NO 140  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 140

Phe Ser Thr Val Pro Pro Thr Pro Pro Ser Ile Thr Ser Thr Gly Leu  
 1 5 10 15

Thr Ser Pro Gln  
 20

<210> SEQ ID NO 141  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 141

Pro Thr Pro Pro Ser Ile Thr Ser Thr Gly Leu Thr Ser Pro Gln Thr  
 1 5 10 15

Glu Thr His Thr  
 20

<210> SEQ ID NO 142  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 142

Leu Thr Ser Pro Gln Thr Glu Thr His Thr Leu Ser Pro Ser Gly Ser  
 1 5 10 15

Gly Lys Thr Phe  
 20

<210> SEQ ID NO 143  
 <211> LENGTH: 20  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 143

Thr Asp Thr Ser Ser Ala Ser Thr Gly His Ala Thr Pro Leu Pro Val  
 1 5 10 15

-continued

Thr Ser Leu Ser  
20

<210> SEQ ID NO 144  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 144

His Ala Thr Pro Leu Ala Val Ser Ser Ala Thr Ser Ala Ser Thr Val  
1 5 10 15

Ser Ser Asp Ser  
20

<210> SEQ ID NO 145  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 145

Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr Pro Pro Ala His  
1 5 10 15

Asp Val Thr Ser  
20

<210> SEQ ID NO 146  
<211> LENGTH: 20  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic peptides

<400> SEQUENCE: 146

Ser Leu Ala Ser Gln Ala Thr Asp Thr Phe Ser Thr Val Pro Pro Thr  
1 5 10 15

Pro Pro Ser Ile  
20

What is claimed is:

1. A panel of glycopeptides comprising at least a plurality of isolated glycopeptides, each isolated glycopeptide comprising a glycopeptide epitope, said epitope having been previously determined (i) to be selectively recognized by a subset of antibodies in sera from cancer patients, which subset recognizes neither (a) the corresponding naked peptides of said panel when not glycosylated; nor (b) the corresponding glycan when not bound to said peptide; and (ii) not to be recognized by antibodies in control sera, said plurality comprising at least 8 isolated glycopeptides, wherein said plurality comprises isolated glycopeptides comprising amino acid sequences of SEQ ID NOs: 86, 109, 116, 132, 134, 135, 145, and 146, wherein said glycopeptides are immobilized on said panel.

2. The panel of glycopeptides of claim 1, wherein the plurality of isolated glycopeptides comprises SHHSDES-

45 DELVTDFPTDLPA (SEQ ID NO: 15); TPTPKEK-  
PEAGTYSVNNGND (SEQ ID NO: 36); SESFHPG-  
FNMSLLENHTRQ (SEQ ID NO: 49);  
LAKMYSAVEPTKDIFTGLI (SEQ ID NO: 86); TDCGG-  
PKDHPLTCDDPRFQA (SEQ ID NO: 109); PGTSTTPSQP-  
50 NSAGVQDTEM (SEQ ID NO: 116); TKTDASSTHH-  
STVPPLTSSN (SEQ ID NO: 132);  
HDVETQFNQYKTEAASRYNL (SEQ ID NO: 134);  
ASRYNLTISDVSVDVPPFPF (SEQ ID NO: 135); VPVTR-  
PALGSTTPPAHDVTS (SEQ ID NO: 145); and SLASQAT-  
55 DTFSTVPPTPSI (SEQ ID NO: 146).

3. The panel of glycopeptides of claim 1, wherein the plurality comprises at least 8 and up to 30 isolated glycopeptides, wherein the plurality comprises isolated glycopeptides having amino acid sequences SEQ ID NOs: 86, 109, 116, 132,  
60 134, 135, 145, and 146.

\* \* \* \* \*